THE
JOURNAL OF MENTAL SCIENCE

[*Published by Authority of the Royal Medico-Psychological Association*]

No. 448 [NEW SERIES NO. 412] MAY, 1961 VOL. 107

Original Articles

THE THIRTY-FIFTH MAUDSLEY LECTURE: "HYSTERIA 311"*

By

ELIOT SLATER, M.D., F.R.C.P., D.P.M.

Physician in Psychological Medicine
National Hospital, Queen Square, London

PERMIT me to begin by saying how pleased and proud I am to have received the invitation to deliver this year's Maudsley lecture. This is, I think, one of the highest honours that our psychiatric confraternity can confer on any of its members, and is something that the recipient will treasure as an enduring reward.

Henry Maudsley, whom we commemorate today, advanced the psychiatry of his time by applying philosophical ways of thought to clinical observations on individual patients. Experimental and statistical techniques in his day were little understood, and psychiatry itself was not yet ripe for their application. The situation is now a very different one; and we have reached the stage where work which does not rely on one or more of the powerful techniques now available is likely to be received both by editors and by the generality of readers in a spirit of no enthusiasm.

It is, therefore, with some trepidation that I venture to offer you a discourse which is based on observational data of a solely clinical type. These data have, indeed, been accumulated on a genetical principle, the hypothesis that monozygotic twins offer a controlled experiment set up by nature. But the limitations which apply to all purely clinical studies still obtain. However, there are certain rather primitive questions for which clinical studies are still the appropriate instrument. Controlled experiment and delimited statistical survey are the methods needed for problems which can be isolated and precisely defined. Until we can say just what it is we want to know, exploration along a wide front is still the most promising approach. This is, I submit, still the case with the neuroses; and of all the neuroses perhaps to the greatest degree in hysteria. If I have to trouble you with case presentations, which will lend an anecdotal air to my remarks, I must ask for your indulgence; I know no other way to make my points.

* Delivered before the Royal Medico-Psychological Association, 18 November, 1960.

Collection of Material

The twins which are the subject of this report were collected, as part of a systematized unselected series of all twins with a neurotic or psychopathic diagnosis, from the in-patient and out-patient material of the Bethlem and Maudsley Hospitals between 1 March, 1948 and 31 December, 1958, and from Belmont Hospital between 1 November, 1950 and 30 June, 1953. The Bethlem-Maudsley group in the present study includes all those and only those twins, with a twin partner of the same sex who had survived into adult life, who in the records were at any time allotted the diagnostic classification number 311 of the International List of Diseases (1947), "Hysterical reaction without mention of anxiety reaction", with one further case (DZ 5) who had been given the number 320.7, "Pathological personality NOS" and specified as "hysterical". The Belmont diagnoses which were accepted for inclusion were those of "hysteria" and "anxiety-hysteria".

I would like here to express the gratitude of our Unit to both of these hospitals, and to all the many colleagues whose ungrudging co-operation has made this work possible. If at times I suggest corrections of their views, such as a revision of diagnosis, it must be understood that all I claim is the easy advantage of the observer who can be wise after the event.

The preliminary case-work on these cases was largely carried out by Mr. James Shields, my colleague in the Genetics Unit at the Maudsley. But for the last three years Miss M. Malherbe has undertaken a complete review of all the data obtainable on the neurotic twins, filling in gaps in our information and securing interviews with the surviving patients and their twins. Diagnosis of zygosity has been made on the basis of history, physical comparison, blood-groups, finger-prints and the P.T.C. test. In the series reported there is only one case (DZ 5) in which there is any material doubt that this diagnosis might be incorrect.

Concordance

The most striking of our findings is that, in the 12 MZ and the 12 DZ pairs, there is no single twin partner of all the 24 probands who has at any time received a formal diagnosis of hysteria. The nearest approach to such a diagnosis is found in one of the dizygotic pairs (DZ 9).

> The family background of this pair was a curious one. The father was a manic-depressive with several hospital admissions, and in addition a crank who ran an unsuccessful campaign for the revival of craftsmanship among country blacksmiths. The mother was his first cousin, with further manic-depressive illness on her own side of the family, and must have been as cranky as he was. When the Proband was taken to the Child Guidance Clinic at the age of 11, the psychiatrist noted that the little girl prattled to him about coprophilia and of her twin sister's inferiority complex and infantile attachment to the father. She was regarded as an anxious self-dramatizing girl, but was not then diagnosed as a hysteric. However, it was the Twin who was first taken to the CGC some months before her sister at the age of 11, and again later between 13 and 16. She was then regarded as "an unstable adolescent with hysterical and depressive traits, reacting to an abnormal environment"; but the depressive aspect was thought more important than the hysterical one.
>
> The Proband was diagnosed as a hysteric when she was treated in the Maudsley at the age of 18. She had become depressed and unable to go on

with her studies at the university, and was self-reproachful and agitated, picking her hands and biting her nails. Several suicidal attempts were thought to be histrionic. Her illness was put down to a romantic attachment to a psychopathic criminal, who was shortly expecting release from prison. She was treated with psychotherapy and improved, but two years later was back again, now four months pregnant by a Ghanaian student. There is a suggestion in the case record that the earlier depression had been succeeded by a mildly hypomanic state, involving the patient in her pregnancy. If that is so the whole cycle may have been a cyclothymic one.

If we can accept this pair as a concordant one, we must calculate the concordance rate for hysteria as 0 per cent. in the MZ pairs, 8 per cent. in the DZ pairs, which is far from impressive evidence of any specific genetical causation. We may, however, cast our net somewhat wider, and consider whether there are further cases of neurosis among the twins. In fact, three of the MZ and one of the DZ twins have come under psychiatric observation for this cause (MZ 2, 10, 12, DZ 1). One of these (MZ 2) may be taken as an illustration.

This pair, also, come from a family in which endogenous depressions have occurred. From the beginning the Proband was a little behind his twin in development and vigour, but they were both forward children. They won scholarships to grammar school and university, and were on the point of starting at their universities in 1939 when the war came. Both registered as conscientious objectors, and were assigned to such duties as land drainage and civil defence. This was too much for the Twin, who according to his mother, decided he must get out and organized himself medical discharge on grounds of psychoneurosis. The patient might have had more cause for this. He had had a mild depression at the age of 16 after the death of his father, and another depression lasting three months in 1943. However, he stuck it out, and served his time.

After the war both returned to their universities. The Twin completed his three years, got his B.A., and through a varied and adventurous career, till recently in the theatrical world, has never had any later neurotic episode. The Proband, however, got behindhand with his studies, and as the finals approached began to fear he would not even get a good pass and would be left without means or profession. He could not concentrate, had difficulty even in talking, and had symptoms of depersonalization such as the feeling he was doing everything "second-hand". On the day of the finals he did not present himself, but had an amnesic fugue lasting six hours. A few days later he was admitted to the Maudsley, underweight and depressed, but without other abnormality. Psychotherapy and a modified insulin treatment brought improvement. After discharge he was recommended to come up for further psychotherapy, but did not, and improved to recovery without further aid. He went back to his studies for a time, but eventually gave up without taking his finals. Ever since he has been perfectly well.

In this case the hysterical dissociation seems to have occurred under psychogenic pressure, but also at a time when powers of adjustment were impaired by a state of depression. Dealing very briefly with the three remaining pairs in which there is technical concordance in respect of neurosis, we have (MZ 10) a pair of psychopaths with numerous hysterical personality features, of which the Proband has a long history of hospital attendances, the twin a single episode when he was invalided out of the Army for psychoneurosis, having lost his memory after a fall. The second (MZ 12) is a pair of boys, now

21, who from earliest years have been of dull intelligence, enuretic, truants, subject to a number of neurotic traits, and with long records of delinquency, and with hysterical symptoms such as faints, falls and visual hallucinations. Characterologically they are almost mirror images of one another, but it is only one who achieved a psychiatric diagnosis of hysteria. The third case (DZ 1) is one in which the Proband is a severely psychopathic woman, her twin much more normal with a single illness, with symptoms of an anxious and depressive type, from which she recovered spontaneously in four months.

So far, then, we have 3 MZ pairs and 2 DZ pairs concordant for neurosis, giving us concordance rates of 25 per cent. and 17 per cent. Neurotic states, however, are not infrequently handled entirely by the family doctor, with or without referral to general hospitals, and never reach the psychiatrist at all. In this series there are four cases in which this has occurred (MZ 6, 8, DZ 2, 3). In the first of these the Proband is a higher civil servant who, after many years of work and war service in the Far East, found himself at the age of 38 reacting badly to the stresses of a very responsible post. He complained of headaches, depression, inability to concentrate and a head that seemed full of cotton wool. He worried about a sister-in-law who had been under treatment for cerebral tumour, and the psychiatrist considered his illness hysterical, presumably on the basis that it was the product of suggestion. He arranged, himself, to get psychotherapy, but despite it remained ill for four years, having to be off work for 6 months three years after the first onset. Eventually he made a fair recovery. His less brilliant twin found himself a much easier and less ambitious life, but also had an unexplained illness which started about a year later than that of his brother. The main symptom was lassitude, but after a time he also complained of an unpleasant smell in the nose. Moving in less sophisticated circles than the Proband, he was satisfied with treatment along ordinary medical lines; but he remained ill until an antropuncture a year after the onset put an end to the smell in his nose.

The other monozygotic pair which falls into this group (MZ 8) is one in which the Proband had an industrial neurosis with difficulty in walking, which lasted about 2 years, and kept him off work for a year. His twin was a bus-driver, who was unable to walk for a fortnight after a road accident in which a man was killed.

If we are to include these cases also in our concordance figures, we have 5 concordant pairs among the MZ twins, and 4 concordant pairs among the DZ. The difference is still negligible, and again we are driven towards the conclusion that specific hereditary factors are not manifesting their presence. We have not entirely covered all the psychiatric abnormalities among the twins of our probands; the list is complete with mention of a schizophrenic (MZ 11), a mental defective (DZ 8), and a ne'er-do-well with a criminal record (DZ 11).

Family History

Our effort, then, to track down one type of aetiological factor, the genetical one, through the aid of concordance figures, appears to have taken us very little distance. Similarities of personality are often far-reaching, but are rather seldom brought to the fore in symptomatology. Furthermore, despite the totally different genetical situation in MZ and DZ twins, in this group there is little difference between the two kinds of twins, whatever the criteria we employ. There is one further step we can take along genetical lines, and that is an examination of the family history.

In his valuable monograph on Hysteria, Ljungberg (1957) calculated that the incidence of hysteria in the fathers, brothers and sons of hysterics was approximately 2, 3 and 5 per cent. and in their mothers, sisters and daughters 7, 6 and 7 per cent. For the general population he gives a morbidity risk of 0·5 per cent. The findings, he thought, supported the view that polygenic factors were responsible.

Ljungberg provides a life-table showing the distribution of morbidity risk of hysteria with age. Using this, we can calculate that in the 23 fathers, 24 mothers, 43 brothers and 29 sisters of our probands we have observed the equivalent of 96·31 life-times of risk. Among these first-degree relatives there is no single individual who has ever been diagnosed as having a hysterical illness. However, two mothers can be written down as having abnormal personalities of a hysterical kind, and one brother is an abnormal socially poorly adjusted individual who, I think, would have been classified by Ljungberg as a hysteric. The incidence of hysteria, on these criteria, is then approximately 3 per cent. This fits in fairly well with Ljungberg's own figures. Another way of putting it is to calculate that, if the incidence of hysteria among the relatives of my probands had been the same as in Ljungberg's group, I could have expected to find 4·2 hysterics among them, with which the observed 3 agrees fairly well.

Ljungberg found no significant increase in the incidence of other psychiatric disorders among the relatives of his propositi, but there was such an increase in the propositi themselves. Among his male hysterics he found 3 who were schizophrenic, and among the females 5. The incidence of schizophrenia in the propositi themselves was, therefore, 3·1 per cent. In addition there were 1 male and 4 female manic-depressives, i.e., 2·4 per cent.; and 4 male and 8 female epileptics (3·3 per cent.). All these figures are high, and although individually they are not very significant, together they are impressive. Ljungberg states that the total incidence of psychoses among his propositi, that is including schizophrenia, manic-depressive psychosis, presenile and senile psychoses, psychogenic psychosis and undiagnosed psychosis, is 9·9 per cent. for men, 9·5 per cent. for women, diverging significantly from the expectation for the general population of 3·1 and 3·2 per cent.

Among the relatives of my probands I found no schizophrenics, and only two epileptics, a brother and a sister. There was, however, a noteworthy number of manic depressive and typically endogenous affective psychoses. There were no fewer than 5 well-established cases, 3 fathers and 2 mothers; and in addition one mother and one brother are of cyclothymic personality, one sister possibly had a depressive illness, and one mother had a depression diagnosed as reactive, but quite probably predominantly endogenous. If we take the risk period as lying from 20 to 65 in the male and 20 to 60 in the female, we may calculate that 69·5 risk-lifetimes have been observed, against which 5 sure cases represents an incidence of 7 per cent.

Among his propositi Ljungberg found that nearly half of both the men and the women had shown abnormal personalities, hysterical, asthenic and psychoinfantile types predominating. However among the first degree relatives there was no great incidence of psychopathy, as judged by fairly strict criteria, 4·9 per cent. among parents and 2·6 per cent. in siblings against an expectation of approximately 3 per cent. Among the relatives of my probands 2 fathers, 4 mothers and 1 brother were personalities abnormal to the point of psychopathy; but 3 of these individuals have already been classified as hysterics, so that we are left with an approximately 4 per cent. incidence of non-hysterical psychopathy among the parents. In addition, one each of the fathers, brothers

and sisters, and 3 of the mothers, could be regarded as showing hysterical traits of personality within normal limits.

The findings are, therefore, largely what might have been expected on the basis of Ljungberg's work, with the single exception that in this series the cyclothymic constitution shows up in a remarkable way. There is no indication that hysteria (or 'hysteria 311') can claim the autonomy of a genetical syndrome.

Early Environment

Let us then turn to the environmental determinants, beginning with those that arise in infancy. There are two findings here which are interesting. In the dizygotic pairs, in all 8 cases where a difference in birth weight is known, it was the proband who was the lighter; and of the 6 cases where there was a noteworthy difference in health in childhood, in 5 cases it was the proband who was at a disadvantage. No such systematic difference shows in the MZ pairs. Both these findings suggest the significance of physical factors operating in early life; but as the differences between proband and twin are confined to the DZ pairs, we cannot exclude the possibility that these physical factors may have a genetical basis. Finally, a striking finding is that where there was a difference in handedness, in 3 MZ and 3 DZ pairs, it was the proband who was left-handed or ambidextrous. The probability of such a finding arising by chance is one in 64. This, too, is a feature which may be speculatively connected with an organic predisposition.

Sometimes, in the individual case, it is possible to be a little more precise. Thus in one of the DZ pairs (DZ 6), the proband at the age of 13 was away from school for a year, and in hospital for 4 months, with an illness involving jerky movements, provisionally diagnosed as chorea and finally as habit spasm. Recovery was very gradual when she was taken to the seaside to live with an aunt. The mother does not remember nervous traits before this illness; but according to another source both twins had neurotic symptoms before this age. In the Proband anxiety attacks started at the age of 19. A feature of her illness was that whenever she became emotionally upset, numbers of jerky and tic-like movements would appear. The development of the illness was most unfavourable, the patient ruthlessly exploiting her symptoms to dominate her environment. but it seems to me by no means out of the question that a post-choreic personality change of an organic type partly laid the ground for her hysterical disposition.

A diligent search for other factors which might have played a part, such as birth order, birth difficulties, differences in breast feeding, in early development, and in parental attitude, and twin leadership, etc., have brought no quantitative differences between proband and twin to light.

Bodily Health in Adult Life

We receive an indication that this may be of moment in the observation that in the MZ pairs 5 of the twins enjoyed rather better health than the proband, the opposite being seen only once. In the DZ pairs the difference is more striking; in 9 cases the twin had the generally better health, and there is no case where the proband had the advantage. One way in which physical illness may predispose to hysterical symptoms is illustrated by MZ 3. The only noteworthy difference between the twins in this case is the amount of illness suffered by the Proband, gastric and intestinal trouble, cystitis, etc., which seems to have had a genuine physical basis; when her physical health improved, the hysterical symptoms passed off. However, differences are more quantitative than qualita-

tive, and there is only one case (DZ 8) in which a physical factor played a recognizably decisive role.

In this case the Twin, who is a mental defective, has stayed at home and has had no physical illness. The Proband had otitis media and later mastoid disease. She had in all six mastoid operations, then a labyrinthotomy, and finally in 1953 at the age of 35 an operation for drainage of a tempero-sphenoidal brain abscess. There was delay in healing, and she was suspected of interfering with the ear and stirring up infection whenever her work as a nursing sister got beyond her. Her matron regarded her as having exhibitionist tendencies. She did her work well, but had too much sick leave. On one occasion she was found to have "large quantities" of barbiturate drugs in her possession, and was thought to be taking them to excess. Her neuro-surgeon referred her to a psychiatrist with a note that "although she recently had a brain infection with *B. coli* abscess in the brain, I think there is no doubt that many of her symptoms are not organic in origin". The psychiatrist thought she showed organic intellectual deterioration, with indications of a nominal dysphasia, also an absence of insight not wholly explained as a hysterical reaction. Psychometry confirmed impairment of memory, learning difficulties and some nominal dysphasia.

She was admitted to hospital in an excitable, talkative, emotionally labile and rather euphoric state. She felt that her condition had been neglected and was "self-righteous and sanctimonious, naïve and exhibitionistic". She rejected any suggestion of self-injury. The diagnosis was "Hysteria, ? self-injury". Two weeks after admission her ear began to discharge, and for an interim of a fortnight she was transferred to an E.N.T. hospital. After her return she continued to run an intermittent temperature. At times she seemed little bothered by her own illness, at other times she would complain of pain in the ear, and hint that more investigations should be done.

Perhaps the poor girl was right. She went home in September, 1953, and died a year later, the post-mortem revealing that a large abscess in the left temporal lobe had ruptured into the ventricles. There was very little infection in the middle ear.

In this tragic case there can now be little doubt that the whole of the illness was attributable to the chronic cerebral abscess, which was never effectively treated. The hysterical colouring to the case, which led to unworthy suspicions of the Proband's integrity both as a patient and as nurse, was presumably derived from the personality. Before her illness she was a rather over-enthusiastic humourless person, attracted into nursing by a genuine idealism. Brain changes in the temporal lobe probably made her more labile, sensitive and difficult. The bad relations which developed between the patient and her medical advisers seem a not unnatural result of pressure on her side to get more effective treatment, and despair on theirs about how that could be provided.

Epilepsy

Among his group of hysterics Ljungberg found 3 per cent. were epileptic. The suspicion that epilepsy has provided the basis of a hysterical predisposition arises in a number of cases in the present material. One of the most interesting is MZ 7, in which the Proband suffered from faints from adolescence onwards. One is tempted to regard them as having been vaso-vagal, since low blood-pressure runs in the family, and the Proband's blood-pressure has always been

very low, when taken in hospital 80/50, as against her twin's 115/70. Her psychiatric history is long and complex, with hysterical symptoms such as aphonia, talking in sleep and a trance state at different times. However, at the age of 44 at last follow-up, she was having attacks occurring almost entirely at night in her sleep, with bladder incontinence, and was being treated with epanutin.

Two of our probands had epileptic siblings. In one of these (DZ 1) the patient suffered from attacks of giddiness and faintness, but showed nothing else to suggest epilepsy. In the other (DZ 7) the patient had atypical fits at the age of 11, leading to an examination at the National Hospital and the conclusion that they were not epileptic. At 25 she had a severe anorexia nervosa, so intractable that after 3 years she had an anterior leucotomy. After this the fits recurred and persisted despite anticonvulsants. EEGs showed numerous slow and fast waves, but nothing specific of epilepsy. Some attacks were observed, and regarded as tetanic and produced by over-breathing. At the age of 31 she had a second leucotomy. At follow-up this year, aged 38, she is once again having fits about once a month. She has a walking disability of the grossest hysterical kind, but also a mass of obsessional rituals. Her state suggests a progressive cerebral process.

Apart from these cases, blackouts, attacks of going limp, dizzy attacks, faints, falling attacks, short lapses of memory, have been observed in 6 MZ cases (1, 4, 5, 8, 9, 12) and in 4 DZ cases (2, 4, 5, 10). In one of these (DZ 2), the patient was found to have a very unstable EEG, and metrazol produced a burst of typical spike and wave suggestive of epilepsy. In another case (DZ 10) the patient's illness, which was depressive in form, was preceded some months previously by the occurrence of two epileptiform attacks on the same night. The general practitioner was sent for, and found her semi-conscious, having bitten her tongue.

Not very many of these patients have had any EEG examination, and those that have showed only non-specific anomalies. However, considering how atypical a temporal lobe attack can be, and how much EEG investigation is often required to demonstrate a temporal lobe focus, it seems to me far from improbable that more thorough and systematic examination would have brought to light some unmistakably positive findings. One of the probands (DZ 12) was under my own care in the National Hospital with a state of agitation and depression, in which she complained of overwhelming sexual feelings and the continual recurrence of spontaneous orgasms. Though I was unaware of it at the time, the symptoms were very similar to those of the well-known case of Erickson (1945) of angioma of the paracentral lobule; and the temporal lobe epileptics of Van Reeth *et al.* (1958) had comparable sexual experiences.

Schizophrenia

Among his 381 propositi, Ljungberg found 3 males and 5 females who were schizophrenic. In the present material there is also a schizophrenic (MZ 11) These twins were dull and backward boys who became schizophrenic within a year of one another between the ages of 22 and 23, in 1957. They are now both chronic patients in mental hospitals. When the Proband was admitted to the Maudsley Hospital he had shown a personality change and catatonic symptoms for three months, and had had delusions, such as that the sound of passing cars was that of aerial activity indicating the imminence of war. However, such symptoms were to some extent in abeyance while he was in the

Maudsley, and the foreground of the picture was taken up by a hysterical pseudodementia. Asked in digit retention to repeat 246, he gave 358. He said 2+3=6, 3+3=5, 4+2=7, that there were 13d. in 1s. and 21s. in £1. On a later occasion he denied all knowledge of his home address, his brother and his previous career, and even said he did not know his own name; but he now said there were 12d. in 1s. and 20s. in £1. Asked why he had got the answers wrong before, he said "Joking, doctor, just for a joke". Asked why he had been walking round with an empty wheelbarrow, he said, "An empty wheelbarrow is easier than a full one; I don't like heavy work." In short the picture, which was of very temporary duration, was that of a Ganser state or buffoonery syndrome. These states have attracted much psychiatric attention from time to time, and have been found to be of very various aetiology, schizophrenia accounting for a certain number.

Endogenous Depression

Ljungberg found 5 manic-depressives in his group, and in the first two case histories I quoted there are grounds for thinking that hysterical symptoms arose in the course of an endogenous depression. These are not the only ones. The illness of the proband in MZ 6, already quoted, was depressive in symptomatology, and the principal justification for a diagnosis of hysteria was the belief that the patient's headaches were the product of suggestion. A fourth case is that of DZ 10, whose illness, depressive in form, came on in the puerperium shortly after a stillbirth. A fifth case is that of MZ 4.

> In this case, the patient attended the Maudsley Out-Patient Department at the age of 34 with the complaint that every three or four months he would have 7 to 10 days in which he was dizzy, irritable and taciturn. The attacks came without precipitating cause, and between whiles he would be all right. His wife thought they had started after hearing that an acquaintance had been found to have cancer. Three weeks before attending, the patient had gone to work, had felt bad, and had collapsed at the First Aid post. He had had several slight turns of weakness almost daily since. He slept well, but woke tired, was constipated, got very depressed, and had fears of cancer. On examination, though he looked pale and ill, nothing abnormal was found but a numbness of the shoulder thought to be hysterical. He soon ceased to attend the out-patient department, but follow-up six years later shows that he made a spontaneous recovery and has remained well ever since; in the interview he showed nothing hysterical. The father of this man was admitted to Bexley Hospital with a depression at the age of 62, dying there five years later.

Personality

In his study, Ljungberg assigns a principal aetiological role in hysteria to deviations of personality, and in this he follows excellent precedents. Nevertheless he found that more than half of his propositi had shown no marked deviation of the premorbid personality. The commonest deviant types were the hysterical 21 per cent., the psycho-infantile 10 per cent., and the psychasthenic 8 per cent. Ljungberg further defines these types as follows. The hysterical type shows the suggestibility and distractibility postulated by Janet; he is quick to learn and to forget, with enthusiasm easily aroused but endurance limited; he has a pressing need of variety, and of being the centre of attention; he is subjective and egocentric.

The psycho-infantile type has a strong affective fixation and dependence on his relatives, and needs guidance and help; he shows traits of childishness, is credulous and easily led; under external pressures he is apt to react with a state of insufficiency.

The psychasthenic type easily becomes tired and suffers from anxiety. In order to compensate for a reduced supply of energy, the psychasthenic tends to avoid surprises and choice situations, and often subjects himself to a routine. He is shy, withdrawn, meticulous, dutiful, irresolute and vacillating.

In the present study, I have not subjected these cases to the same analysis. I have not attempted, in fact, to estimate any deviation from an imagined norm. Instead I have tried only to note the particular ways in which probands differed in personality from their twins. Nevertheless the results agree fairly well with those of Ljungberg. with the proviso that the main differences between proband and twin were along the psychasthenic and the psycho-infantile dimensions rather than the hysterical dimension.

The commonest and most consistent difference was for the proband to be the more anxious, worrying and tense of the pair, this difference being shown in 9 pairs in the one direction. It may be quite marked, even in MZ pairs, and then of course is not genetically caused. In one pair (MZ 6) the difference arises as the result of a polar development of the twins; in the rivalry in which they were involved the one who excelled became increasingly ambitious, serious and tense, while his brother gave up all lofty ambition and relaxed into a humdrum career. The important role which tendencies to tension and anxiety have played, not only in the personalities but also in the illnesses of these patients, is illustrated by the fact that two of them have each been submitted not to one but to two leucotomy operations.

Related to the anxiety tendencies, minor perfectionist and obsessional features were shown in 7 probands and in 2 twins; and there was greater social timidity and shyness in 11 probands to 1 twin. Differences in energy and initiative also showed a preponderance, the twin having the advantage over the proband in 11 cases to 4.

Traits which I should call hysterical—excitability, suggestibility, shallow affects, selfishness and self-will, histrionic traits—were about as common as in Ljungberg's material, and were more marked in the proband than the twin in a quarter of the cases (MZ 1, 10, 12, DZ 1, 6, 9). Some degree of hysterical disposition is, however, shown by 4 twins (MZ 2, 5, DZ 3, 10).

From the historical point of view, it was as a rule the proband who was the more neurotic in childhood, and who had more changes of occupation. There were also striking features about their sex lives which to some extent support Ljungberg's emphasis of psycho-infantile traits.

Taking the probands, there are only 3 men and 1 woman who have had fairly normal lives, with marriage to normal partners. Two male and 6 female patients have probably never had any sex relationship at all. Two other women have had difficulties in marriage, one being separated from her husband for a time. All the remainder have chosen odd partners. Of the men MZ 2 married a wife who had been hysterectomized; MZ 4 married a woman who was a chronic neurotic and hypochondriac; MZ 10 married a neurotic woman who later had a paranoid psychosis. Of the women MZ 3 first got engaged to a Canadian soldier who proved to have a wife already, and later married a man who had been in hospital with a schizophrenic illness. MZ 5 married a man who later went to prison for car frauds. Since her divorce she has cohabited with a man she refuses to marry, though she has twice been pregnant by him.

One of these pregnancies was aborted on psychiatric grounds; after the other she arranged to have the child adopted.

In the dizygotic series, DZ 2 married a man who had been deaf since childhood, and who later left her perhaps owing to her illness; this woman was also sterilized; DZ 3 married a man with chronic nephritis who soon became impotent; DZ 7 found her husband through a marriage bureau, a shy and nervous man who dotes on her; DZ 9 fell in love with a criminal psychopath twenty years older than herself, and later had an illegitimate baby by a black man; and DZ 12 married an unsociable rigid man, who is both vegetarian and valetudinarian.

The twins have been more fortunate, but in them too, sex interest which is late or feeble, and failure to marry is found in 10 cases; and two marriages have ended in divorce.

Psychogenesis

It is not easy to exclude the operation of psychogenic factors in any of our cases; but in about half of them it is difficult to put one's finger on anything very particular. If the proband has come under one form or another of psychological stress, the same has been no less true of the twin, and a differential incidence cannot be discerned. In a further 5 cases (MZ 2, 4, 6, DZ 3, 12), we find psychogenic factors obtruding, but with some doubt about the extent to which they have been effective. These stresses are of a banal kind; examination anxiety, an extravagant wife, responsibilities of an exacting post, an impotent husband, a rather unimportant love affair. In two further cases the psychogenic factor exercised a decisive role, but one which would hardly have been effective save for the pre-existing hysterical disposition. Thus the illness in MZ 8 was essentially in the nature of a compensation neurosis; and the repeated fugues of DZ 11 were precipitated by the most trivial embarrassments.

In one case (MZ 5) there was a stress situation of a truly drastic kind. The patient married a man of whom her parents disapproved, and even after the marriage they waged a long, ruthless and eventually successful campaign to part her from him. When she was in the Maudsley, the patient complained she felt in the middle of a battle that was tearing her apart, and that she was being asked to make decisions which were too difficult for her. However, the case was an exceedingly complex one. Both the patient and her unstressed monozygotic twin developed Graves' disease and had to undergo thyroidectomies; the Proband showed an EEG abnormality not shown by her twin; and during her illness she exhibited a depression with diurnal variation of endogenous type, obsessional features and depersonalization. Her after-history was very psychopathic for years after the solution of the acute conflict by divorce.

Four of the cases show a psychogenic situation of a particularly interesting kind, what one might call a form of folie à deux, since two people share the same delusion. We see, as it were, the sick patient on the obverse of a medal, on the reverse side of which is the face of a fellow-conspirator. This figure is that of a member of the family who is busily employed in fostering the illness. Where the patient is female, this individual is commonly a father or husband. Thus in MZ 1 the hysterical development of the Proband's personality can be traced to the father, who preferred her to her twin and after an appendix operation gave orders she was to do no more heavy work. In DZ 4 we find a husband who is dominated by the Proband's complaints, has to come home to comfort her in the middle of the day and is never allowed out in the evening.

In DZ 6 the Proband suffers from attacks of breathlessness, and has had almost continuous psychotherapeutic support for 9 years; the situation is made almost unmanageable by the fact that her father panics if she has one of her attacks, and feels he must be able to give her, at once, all the sedative tablets she wants. In the fourth case (DZ 7) the husband not only works for a living but also runs the house for the patient, looking after her in every way. He is repeating the pattern of behaviour of the Proband's own parents, since her father also did all the work for his supposedly crippled wife.

This situation is one which is commonly met in the cases one calls hysterical, though it is less frequently recognized. The supporting partner, when seen, makes a normal impression, and his attitude to the patient seems, at first glance, to be everything that is proper. The patient and her partner, however, make a closed circuit with one another, isolating them from other relationships, each supplying the other's needs. The effect tends to be very malign; the four cases quoted have periods of continuous and still continuing illness of 15 years, 7 years, 9 years and 11 years.

Course and Outcome

Such long illnesses are seen in only a minority of cases, but they are not uncommon. Ljungberg regards hysteria as a relatively benign condition, and reports that after 1 year only 38 per cent. of patients were still suffering from symptoms, after 5 years 23 per cent., and after 15 years 20 per cent. Looked at in another way, these results are not so encouraging: if 62 per cent of patients recover within the year, less than half the remainder can ever be expected to recover at all. The follow-up results in the present series are a good deal worse. Five of the probands recovered within a year, and a further 7 in periods of 2 to 7 years. To the present time half the patients are still suffering from symptoms, at a mean duration of $5\frac{1}{2}$ years after the critical diagnosis was made.

It is often made a subject for wonder that the psychiatrist does not frequently see patients in middle life who have had hysterical symptoms for many years; and the comforting conclusion has been proposed that this is because the youthful hysteric nearly always gets better. Both Ljungberg's material and the present series show that this is not so. If the psychiatrist does not see these patients in later life, it is because the patients themselves have found out the hollowness of the hopes that he can offer. They have given up attendance at psychiatric clinics, and have learned to rely on the medicines they can get from their family doctors.

Perhaps the most surprising feature of the follow-up statistics is their lack of uniformity. Some patients do well, others very badly indeed; and good or bad outcome bears little relation to the nature, the amount or the severity of the hysterical symptoms. To get a clue to the prognosis, we have to look, not at the hysterical mechanisms exposed, but to their aetiological basis, whether this is a brain lesion, an endogenous psychosis, a deviation in personality development, a temporary stress situation, or a built-in self-perpetuating mechanism.

Conclusion

We have now reached the position when we are compelled to ask, what is the justification for regarding hysteria as a syndrome? The aetiology appears to be very various; and the hypothesis of a genetical basis of a specific or indeed important kind has had to be discarded. Among the hysterics of the present series we have found patients suffering from a focal brain lesion, also probably

from epilepsy, from schizophrenia, from endogenous depression, and from anxiety states falling more easily into the category of affective than hysterical illnesses. Comparative analysis of personalities shows the affected twin not so much more hysterical as more anxious than his partner. Both psychogenic and physical factors play a role in aetiology; but with some interesting exceptions they are of a varied and non-specific kind. The clinical picture is equally various; and the hysterical symptoms which are relied on for diagnosis are always accompanied by others of a different nature. No particular method of treatment seems to be of more general application than any other. Drug therapy, psychotherapy, E.C.T. and leucotomy have been tried, none showing any sign of being a specific remedy; patients get well or remain ill for reasons which are individual and often far from clear.

The one thing which is common to a large majority of the cases we have investigated is that they were very difficult problems clinically; even after prolonged follow-up many remain complicated and obscure. It is certain that some clinicians make the diagnosis of hysteria more readily than others. In some sense it is true to say that "hysteria" is a label assigned to a particular relationship between observer and observed; it appears on the case-sheet most readily if the doctor has found himself at a loss, if the case is obscure and if treatment has been unsuccessful. Of all diagnoses it is that which is least likely to be made in a spirit of detachment. There is a temptation to shelve further enquiry along aetiological lines, if the clinician sees or thinks he can see a histrionic quality in the patient's complaints, if some symptoms can be regarded as lacking genuineness, and if the patient demands rather than accepts treatment.

To be sure, the dissociative mechanisms of hysteria are known of old, and can lead to symptoms which deserve no other name. But the diagnosis of an illness as hysterical goes much further than the recognition of a symptom. The unreliability of the diagnosis indicates the unsatisfactoriness of a psychopathology which is based solely on a mental mechanism. In the past, delimited studies of such conditions as Ganser states and anorexia nervosa have repeatedly shown their heterogeneous nature. It seems permissible to suggest that this principle might be of wider application. The mere manifestation of a mental mechanism within the range of normal potentialities tells us little of consequence. If in our patient we find the signs of hysteria and no more, then these are signs that we have not yet looked deeply enough.

References

Erickson, T. C., "Erotomania (nymphomania) as an expression of cortical epileptiform discharge", *Arch. Neurol. Psychiat.* (*Chicago*), 1945, **53**, 226.

Ljungberg, L., "Hysteria. A Clinical, Prognostic and Genetic Study", *Acta. Psychiat. Neurol. Scand. Suppl.* 112. Copenhagen, 1957.

Van Reeth, P. C., Dierkens, J., and Luminet, D., "L'hypersexualité dans l'épilepsie et les tumeurs du lobe temporal", *Acta Neurol. Psychiat. Belg.*, 1958, **58**, 194.

TABLE I

			Hospital No.	Born	First Saw Psychiatrist	Became Proband	Last Follow Up	Photographs	Physical Comparison	Blood Groups	Finger prints	P.T.C.
MZ	1	f	B 0389	9. 9.06	11.47	5. 3.48	18. 9.58	+	+	+	+	+
	2	m	B 3091	2. 6.20	12.47	10. 8.48	18. 8.60	+	−	−	−	−
	3	f	B 8236	12.12.06	1.50	17. 1.50	22. 8.58	+	+	+	+	+
	4	m	D 0500	10.11.17	2.52	19. 3.52	14. 7.58	+	+	+	+	+
	5	f	D 1058	21. 9.30	3.52	16. 6.52	29.12.58*	−	+	+	+	−
	6	m	D 1345	11. 9.13	2.52	31. 7.52	6.10.58	+	+	+	+	+
	7	f	D 2030	21. 2.14	11.52	29.11.52	1. 3.58*	−	+	+	+	−
	8	m	4211 N	2. 6.15	1.53	19. 2.53	22. 6.60	+	+	+	+	+
	9	f	E 0649	30. 4.32	3.53	8. 4.53	1. 9.58	+	+	+	+	−
	10	m	E 1612	20.10.14	9.53	7. 9.53	3.10.58	+	−	−	−	−
	11	m	J 0121	1. 6.34	1.57	17. 1.57	1. 6.60*	+	+	+	+	+
	12	m	J 1477	30.10.39	1946	23. 7.57	18. 2.60*	+	+	+	+	+
DZ	1	f	B 5387	28.11.30	5.49	3. 5.49	14. 8.59	+	+	+‡	+	+
	2	f	B 6722	26.10.20	9.47	7.10.49	21. 4.60	−	+	−	+	−
	3	f	8247 G	9. 5.22	10.50	15.11.50	12. 9.60	−	+	−	+	+
	4	f	8330 G	21. 9.14	7.50	10. 1.51	29. 7.58	−	+	+	+	−
	5	f	A 7031	5. 1.17	10.46	18. 9.51	30. 9.58	−	−	−	−	−
	6	f	8765 G	22. 6.32	3.51	25. 9.51	4. 5.60*	−	+	+	+	+
	7	f	9543 G	6. 2.22	1949	18. 3.53	9. 5.60*	+	+	+	+	+
	8	f	9624 G	4. 8.17	4.53	12. 5.53	26.10.54†	−	−	−	−	−
	9	f	H 0074	25. 8.37	7.49	12. 1.56	2. 1.59	+	+	+	+	+
	10	f	J 0035	22. 5.32	3.56	7. 1.57	12.10.60	−	+	+	+	+
	11	m	K 0930	20. 2.26	10.55	8. 5.58	16. 4.60	−	−	−	−	−
	12	f	K 1409	8.11.18	7.58	14. 7.58	.7. 4.60	+	+	+	+	+

* Still under psychiatric care.
† Died.
‡ Blood groups identical, P_{DZ} 0·06.

APPENDIX: CASE HISTORIES

MZ 1 (b. 9.9.06). F. d. 63, nephritis, n. M. d. 68, coronary thrombosis, n. Sibs: 1 m. a. 57, n.; 2 m. d. 40, dysentery; presumably neurotic (hysterical). 3 twin. 4 proband. 5 f. d. 2.

Full time, both over 7 pounds, Twin probably bigger. Birth difficult. Twin kept in hospital for 3 months. Both bottle-fed. Both right-handed. Twin nailbiter. Both top class at elementary school. Factory work and various jobs. Menarche: Twin first by 3 weeks; no evidence either has ever had sex relationship. Both have masculine appearance, Twin more so. Wechsler I.Q., Proband 84. Both same childhood ailments. Proband had appendix operation *aet.* 18, and after that father spoilt her, said she was not to lift weights. Twin appendix operation *aet.* 41. Proband always the leader, Twin content to fit in with her wishes and is devoted to her; Proband more obstinate, insists own opinions are right. Both home-bound but keen on church affairs. Both mainly domestic work, and now ward-maids in same hospital.

Proband started to have turns *aet.* 17, go limp, lie quietly, come round after an hour, headache till next day. Once was in a trance for 24 hours; doctor said her limbs would stay put in any position, and demonstrated it. Gradually attacks became less frequent, ceased after *aet.* 24. After appendix operation at 18, Proband developed many food fads. *Aet.* 41 aphonia after death of mother; later recurrence of blackouts, attended Maudsley Out-Patient Department. EEG not suggestive of epilepsy, Twin having much the same record but rather more delta. Improved with psychotherapy 1958. F.U.: 1951–2 for 7 months recurrence of aphonia. 1958 still many symptoms, times when all use goes out of her, headaches, insomnia, lucky if she gets an hour in the night; when seen, is blooming, could not possibly be having so little sleep. Twin in good health but having menopausal symptoms.

Conclusion: Difference between twins psychogenic, especially protective attitude of father and Twin to Proband: polar development of twins, Proband becoming psychopathic.

MZ 2 (b. 2.6.20). F. d. 46 "encephalitis"; *aet.* 45 had depression lasting 3 months till partial recovery leaving him still depressed; a brother suicide in 30s (endogenous depression). M. *aet.* 67, liable to spells of depression, n. Sibs: 1 m. *aet.* 45, irritable, difficult, many changes of job, n. 2 Twin. 3 Proband.

Full time, no difficulties, Twin 7½, Proband 6½ pounds, but Proband heavier by end of 1st year. Proband breast-fed longer. Twin a month ahead throughout infancy. Both right-handed. Proband thought more delicate. Proband a little behind all through school, 2nd or 3rd when Twin 1st. Both scholarships, Twin to Cambridge, Proband to London. Then war, both conscientious objectors, directed to non-combatant duties, Twin organized his invaliding

for psychoneurosis, Proband completed service. Both returned to University, Twin graduated, Proband had amnesic fugue and did not sit finals. Twin went to U.S.A. with teaching fellowship in dramatic art, later University appointment in South Africa, has finally taken post as personnel manager with manufacturer. Twin married 24, 2 daughters; Proband at 25 married a hysterectomized woman, physically rather masculine, but very happy with her. Health: Proband has had more minor illness. In personality Twin always more energetic, socially active and effective.

For history of illness, see text. Admitted Maudsley (In-Patient), 1948 for 1 month. After recovery, tried farming and other jobs; soon obtained post in large bookshop: now head of their classics department, and the job suits him very well. 1960 F.U. Both well.

Conclusion: Difference based on early constitutional difference, Twin tending more to hypomanic diathesis, Proband to depressive. Hysterical dissociation represented real failure of will, but occurred under psychogenic pressure probably during endogenous depressive phase.

MZ 3 (b. 12.12.06). F. d. 75, diabetes, n. M. d. 77, jaundice, n. Sibs: 1, f. *aet.* 54, n. 2. f. d. 49 cerebral embolism, nervous, highly-strung, worries, n. 3. Twin. 4. Proband. 5. m. *aet.* 49, n. 6. f. *aet.* 47, underweight due to nervous dyspepsia, n. 7. m. *aet.* 45, n. 8. m. *aet.* 43, n. 9. m. *aet.* 40, n.

Full term, no difficulties, Proband 7 pounds 2 ounces, Twin 7 pounds; both breast-fed. No differences in health, strength, development; both right-handed. Proband only had perforated ear-drum. Proband more sensitive about being scolded, more emotional. Both backward at school, left at 14 from standard 6. Twin worked as domestic, later as assistant nurse, steadily employed so to date. Proband many jobs as needlewoman, domestic, assistant nurse, factory worker; housewife; now full-time tailoring. Menarche at about same time; Proband always more interested in men, Twin resigned to be single. Proband during war got engaged to Canadian who proved to be married; *aet.* 41 married a man two years younger who had had schizophrenic illness with recovery when 26. One miscarriage; s.i. unsatisfactory. Twin has had no serious illness, though she has had many minor accidents. Proband has had hospital treatment on many occasions 1936–1956 for intestinal trouble, appendicectomy, cystitis, stomach trouble, removal of foreign body, ear trouble.

Proband to Maudsley Out-Patient Department, *aet.* 43, referred by hospital where treated for incomplete abortion. Had a host of complaints, garrulous, talking beside the point, tense, fidgety. On follow-up 1958 found in blooming health, animated, dressed in bright colours, florid gestures and expressions, affect rather shallow. She said that after illness in 1950 she had decided it was up to her to keep cheerful and had succeeded in doing so. Neither the death of a sister in 1954, nor the menopause in 1956 had got her down.

Conclusion: The querulous hypochondriacal state in which the Proband came under psychiatric observation seems most easily accounted for by a considerable amount of bodily illness which preceded it. It is possible that a cyclothymic factor has played a part, contributing to the depressed state of 1950 and the euphoric state seen in 1958.

MZ 4 (b. 10.11.17). F. d. 67, cancer, since *aet.* 62 in mental hospital (endogenous depression). M. *aet.* 73, n. Sibs: 1 and 2, twins, m., f., d. at birth. 3. f. d. 34, asthma, n. 4. m. d. 24, septicaemia, n. 5. f. d. 43 asthma, highly-strung and domineering, n, ? hysterical personality. 6. m. *aet.* 49, n. 7. f. *aet.* 42, n. 7. Proband. 8. Twin.

Full term, no difficulties, Twin lighter and in childhood less robust, but development equal. Both breast-fed. Both right-handed. Both very naughty, nightmares of very similar kind. Both did well at school, Proband slightly cleverer, but Twin was away from school for 5 months, ? T.B. hip. Twin had steady jobs, cable hand; reserved till 1942, then A.B. in Navy, not much action, 1945 machine operator. Proband had great variety of temporary unskilled jobs, 1939–45 in Navy, P.O., now machine operator. Twin married *aet.* 30, 1 son; Proband married *aet.* 25, 2 daughters; wife hypochondriacal, extravagant, poor housekeeper, counters Proband's complaints with her own. Twin liable to headaches, occasional giddy spells (? vaso-vagal), but no psychiatric illness. Proband saw much action in Navy, at Dunkirk, later twice torpedoed, once adrift for 2 days; served his time. Little difference in personality, Twin the more quick tempered, Proband the more adventurous and active. Proband became of more worrying disposition with illness.

For account of illness, see text. Attended Maudsley Out-Patient Department, 1952.

Conclusion: The Proband had much more stress during the war and later had to carry the weight of an inefficient wife. This latter factor may have helped to precipitate an illness which has many of the marks of an endogenous depression. Proband also had turns similar to those of Twin.

MZ 5 (b. 21.9.30). F. *aet.* 54, avoids responsibilities, n., hysterical personality. M. *aet.* 48, domineering maladjusted personality, had untreated nervous breakdown *aet.* 46, insomnia, irritability, hypochondriacal rumination. (Abnormal hysterical personality, menopausal neurosis.) Sibs: 1. Proband. 2. Twin. 3. m. *aet.* 18, asthma, truant, poor adjustment (abnormal personality).

Full term, no difficulties, Proband 3½, Twin 5 pounds. Both bottle-fed and mild feeding problem. Early development equal, later Twin taller, plumper, more attractive; Proband extremely dependent, Twin less so and always preferred by parents, especially mother. Proband left-handed, Twin right-handed. Twin only was liable to screaming fits. From 10–15 twins cared for by strangers in Australia. Twin slightly ahead in education. Both poor work record 17–19; Proband gave up on marriage, after break-up of marriage intermittent work as barmaid. Menarche Twin 15, Proband 17. After thyroidectomy Twin worked fairly well till marriage which proved stable.

The Twin's thyroid trouble began at 18 with loss of interest, irritability, lassitude; hyperthyroidism was only diagnosed after some months. After treatment for 4 years with iodine, thiouracil, etc., she was admitted to hospital in 1952, exophthalmic and 2 stone underweight. Since the operation she has remained well, though still subject to moods of depression and irritability. She worked well till marriage *aet.* 22, which has proved stable, one son. Proband married *aet.* 20, against wish of mother, miscarriage 6 weeks later. She soon started to have faints, visited cardiologists, etc., to no avail. Husband was in R.A.F., and when he was posted away Proband lived with maternal grandmother. When husband visited her he found his letters were being intercepted and determined efforts were being made to separate them.

Proband became pregnant on medical advice, bore daughter January, 1952. While pregnant had screaming attacks, faints, amnesia, aphonia, made threats of suicide. In private hospital, complained of depersonalization, passivity, diagnosed schizophrenic, had 18 deep insulin comas. She returned to live with mother, husband not being allowed into the house. A hysterical fugue led to admission (in-patient) 1952, to Maudsley for 13 months. There bright, cheerful, co-operative, but described diurnal fluctuations of mood, and unreality: things looked two-dimensional and she felt her arms and legs did not belong to her. EEG showed large amount of generalized slow activity. Sleeping pulse-rate 96, B.M.R. +18 per cent. Her marriage now broke up and she went to live with parents. Thyrotoxicosis definitely diagnosed January, 1954, and in May thyroidectomy. Re-admitted Maudsley (in-patient) 1954 2½ months. Subsequent history stormy; 1955 serious attempt at suicide after unhappy love affair; 1956 treatment with thyroid; obsessional fears of killing baby daughter; rupture with mother to leave home and work as barmaid; 1958 now living with a man whom she refuses to marry; her daughter is being brought up by Proband's mother; has had 2 further pregnancies (illegitimate), one terminated on psychiatric grounds, after the other, 2nd daughter adopted. On follow-up 1958 more mature, obsessional fears of harming daughter only persisting symptom. Twin reported well.

Conclusion: The difference between the twins, both developing Graves' disease but only the Proband showing a severe and lasting hysterical personality development, can be largely attributed to psychogenic factors, especially the attitude of the psychopathic mother.

MZ 6 (b. 11.9.13). F. *aet.* 78, fussy, over-serious, n. M. *aet.* 84, n. Sibs: 1. maternal ½-sibling, f. d. 24, n. 2. Proband. 3. Twin. 4 and 5. twins: 4. m. *aet.* 44, life-long bad stammer, n.; 5. m. d. at birth.

Full term, birth difficult—no details. Both 8 pounds, Proband heavier. Both breast-fed. Both precocious, no difference in early development. Both ill as babies with bronchitis, Twin only just saved. Both right-handed. Both stammered, Proband worse and into adolescence. Both good at school, Proband slightly ahead. Proband with scholarship to Cambridge, 1st class honours arts; Twin scholarship to London, science for 1½ years, but broke off to take examination and enter Civil Service; during war P.O. in R.N.; returned to Civil Service post but in the 40s took technical managerial position in agricultural firm. Proband went to Far East, manager of timber firm, joined Territorials, war service, rapidly promoted to Lt.-Col. in Intelligence; after war by special vacancy into higher Civil Service. Twin always much more keen on girls, married 24, 4 children; Proband married 36, no children. Health: despite amoebic dysentery, also a tendency to headaches, Proband has had better health; Twin pneumonia and pleurisy, many minor complaints, health conscious, afraid to take coat off in garden in case he sweats.

1958 follow-up by letter: Proband returned to duty 1956, at present serving abroad, Twin remains in good health.

For history of illness, see text. Attended Maudsley Out-Patient Department 1952.

Conclusion: Difference between twins due to polar development; Twin finding himself consistently excelled by Proband from early years, soon gave up trying. Proband became artistic, idealistic, austere, teetotal, serious; Twin mundane, cynical, self-indulgent, placid, less worrying. Owing to greater ambitions, Proband subjected himself to greater stresses. Both are hypochondriacal, and illness in both is affective (anxiety-tension state) rather than hysterical.

MZ 7 (b. 21.2.14). F. d. 75, heart, n. M. d. 75, stroke, highly-strung, irritable, n. ? hysterical personality. Sibs: 1. Proband. 2. Twin. 3. m. d. 34, ? cause, easily worried, emotionally labile, goes white with anger, n.

Two months premature; very difficult birth, especially for Twin nearly strangled by cord. Twin liable to cyanotic fits for some months. Proband 3½, Twin 2¼ pounds. Twin remained smaller, more delicate. Development equal. Proband left-handed, Twin right-handed. Both

stammered from 9 into adult life; Proband screaming attacks, Twin fear of dark. Proband ahead at school but later slipped behind, graduated English and French; Twin qualified in medicine and in steady salaried posts since. Proband after some years as clerk eventually qualified as social worker. Neither ever any interest in men. Health: at adolescence Proband grew fast, became tall, stooping, leptosome; Twin grew more slowly, never so tall, more pyknic; septal heart defect; successful cardiac operation *aet.* 43. Proband very low blood pressure all life, in Maudsley 80/50; Twin normal, when measured 115/70, after adolescence much more energetic. Proband 15 pneumonia, 30 appendicitis, 31 breast abscess and septicaemia, 40 leaking duodenal ulcer, 44 nocturnal fits with incontinence. In personality both very home-bound but Proband completely dependent on family, especially on Twin. Proband shy, reserved, worrying, no friends, quick-tempered. Twin more energy, vivacity, interests, self-reliance.

Proband admitted to Maudsley (in-patient) 29 November, 1952 for 7 months; depressed for 3 months; had had faints for 18 years, at times up to 2–3 a day, once free for a year. Attacks preceded by nausea or flushing, feels hot and sweats, falls but may break fall, has hurt herself, said to be unconscious up to 2 minutes, has had attacks on own and in company, usually sleepy after attack, no incontinence or tongue biting; has worried whether she had epilepsy. 1951 aphonia for 2 days. Nightmares all her life. Tall, stooping, tic movements of face, neck, trunk. Had 91 hours psychotherapy. Left improved but nightmares continued. 1954 haematemesis and melaena, treated for ulcer. Renewed breakdown when mother had stroke: faints, lethargy, talking in sleep; temporary cessation after laying-on of hands by minister. 1958 follow-up by letter, having nocturnal attacks with incontinence, being treated by epanutin. Twin well.

Conclusion: Difference between twins due to acquired constitution, especially low blood pressure; Twin's higher blood pressure possibly connected with her congenital heart lesion. There is a possibility that throughout the Proband may have been epileptic as well as a severely hysterical personality.

MZ 8 (b. 2.6.15). F. *aet.* 74, dull, paranoid, n. M. d. 32, influenza, Proband being then *aet.* 2, invalid since his birth, n. Sibs: 1. m. *aet.* 54, n. 2. f. *aet.* 51, n. 3. f. *aet.* 49, n. 4. Twin. 5. Proband. Paternal ½-siblings: 6. f. *aet.* 41, n. 7. m. *aet.* 34, n. 8. f. *aet.* 28, n.

Difficult instrumental delivery; Twin heavier. Not breast-fed. Twin always stronger, Proband "consumptive bowels". Both right-handed. Twin headaches as child. They were separated and brought up in different homes. Twin's home happy; Proband very unhappy, cruelly treated, locked in dark room without food; described as sullen; 2 attempts to run away at 14; 17, ran away. At school equal. Both mainly labouring jobs, Twin eventually bus-driver, Proband clerk. Both married at 24, Twin no children, Proband 2 daughters; both rather dominated by their wives. Health: Twin nothing serious, Proband malaria, repeated attacks appendicitis. When measured 1954 Twin 185·5 cm., 13 stone 3 pounds, androgyny 97·2; Proband 166·8 cm., 8 stones 6½ pounds, androgyny 91·5. In personality Twin placid and easy-going, Proband anxious, much pre-occupied with childhood unhappiness; Twin more initiative and more effective. 1960 F.U. Both well; Proband now 10 stones 2 pounds.

For illness see text. Admitted Belmont (in-patient) 1953 for 3 weeks.

Conclusion: Differences between twins essentially psychogenic, leading in Proband to development of an anxious personality.

This case awaits publication in greater detail by Mr. James Shields.

MZ 9 (b. 30.4.32). F. *aet.* 59, n. M. *aet.* 53, n. Sibs: 1. Twin. 2. Proband.

Three weeks premature; no difficulties; Twin 4½, Proband 4 pounds; both bottle-fed. Proband ahead at milestones. Twin right-handed, Proband left-handed. Both delicate, over-protected. Both tutored at home. Both to grammar school, Proband scholarship, Twin fee-payer. Twin first to study music, but Proband followed. Both school-teachers, and now in same secondary modern school, sharing a flat. Neither has ever had any boy friend; Twin was more accessible, but Proband would always intervene. Health: Twin more trouble with discharging ear than Proband, at 19 pleurisy and "spot on the lung". Proband jaundice and bronchitis in childhood, all life liable to faints. Proband dominant in twin relationship, but Twin more out-going and accessible; both wrapped up in each other. Strikingly similar personalities, intense, anxious, humourless, though they think they are very different.

Proband attended Maudsley Out-Patient Department a few days before she was 21. Since at 18 she had seen a girl faint in class she had started to faint herself—feel dizzy, sight black out, lose consciousness and fall; attack witnessed, not epileptic; EEG normal. Two sleep-walking episodes. Never disabled or off work for more than a day. Twin says she never faints, but fainted when her blood was taken. 1958 (follow-up by letter) *aet.* 26, Proband's faints still continuing, notably after recent operation for slipped disc. Twin well.

Conclusion: Difference quantitative only, and cause obscure; essentially a case of vaso-vagal instability.

MZ 10 (b. 20.10.14). F. d. 42, chronic nephritis; hypochondriacal self-observer, domineering, could not bear contradiction, outbursts of temper (abnormal personality).

M. *aet.* 63, must have own way, likes to surround herself with admiring subservient men, n, hysterical personality. Sibs: 1. Proband. 2. Twin.

Proband probably heavier; early development equal; Twin regarded as less strong; both right-handed; no neurotic traits recorded. Public school, Proband took lead, Twin sometimes truanted. Proband went to two theological colleges, but gave up; taught in private school where his mother headmistress; later civil service clerk. Twin many jobs, for years shop assistant in jewellers, latterly teaching in mother's school. Proband married *aet.* 28, wife Russian by birth, 1 son. Wife's nervous illness began with air-raid anxiety 1944; by 1949 paranoid, accusing Proband of homosexuality, incest, etc.; subsequently improvement and relapse; marriage continues unhappily. Twin married *aet.* 25, wife plain, from labourer's family; couple ill-matched and marriage unhappy till it broke up. While in army 1940–1946, Proband had much illness including bacillary dysentery and ? malaria; war pensioner.

Attended Maudsley Out-Patient Department *aet.* 38 when sick leave had run out; wife says he is ill often only to get his own way. Since then has had episodes of "pyrexia" (not confirmed), haemoptysis, alimentary disturbances, dizziness, weakness, no energy to work. Very detailed somatic investigations invariably negative. Twin invalided from army after 18 months for psychoneurosis, loss of memory after a fall. He tells fabricated stories of commando trips and strange adventures, made up a document to substantiate his statements. Has added to his names to total of 5 with duplication and hyphenation. Proband regards himself as fey, claims to know when other people are going to die, has the power of hypnosis, once hypnotized himself by mistake by looking in mirror. Both have literary and artistic leanings.

Conclusion: With far-reaching similarities of character structure, twins show sharp superficial difference, Proband being chronic intractable malade imaginaire. The main cause for this difference most plausibly seen in the different health records. Proband having had much genuine and severe physical illness.

MZ 11 (b. 1.6.34). F. no information. M. *aet.* 41, half Chinese, n. Sibs: 1. Twin. 2. Proband. Illegitimate.

Difficult labour, lasted 2 days, Twin first by 1½ days; Proband forceps. Proband immediately to babies' home, from 7 with maternal grandmother. Twin in various foster-homes, adopted at 7. No differences in development known. Both right-handed. Twin walked in sleep, truant, enuretic till 14, set gorse on fire; to C.G.C., *aet.* 10 to E.S.N. school. Proband enuretic till 12, truant, talked in sleep, stole, set fire to papers in cupboard, to neighbour's curtains, to paper tied to dog's tail. Proband in approved school, Twin in probation hostel for stealing; neither can write. Both unskilled labourers. Neither any relationship with women. Both became schizophrenic at 22–23. 1960 F.U. Both still in hospital.

For account of hysterical aspect of Proband's illness, see text. Admitted Maudsley (in-patient) 1957 for 2 months.

Conclusion: Hysterical symptoms in Proband essentially accidental, i.e., product of schizophrenic illness on the one side and intensive psychological investigation while in hospital on the other.

These twins await publication in greater detail by Mr. James Shields.

MZ 12 (b. 30.10.39). F. *aet.* 51, emotional, quick-tempered, somewhat of a dodger, inconsistently thrashes or ignores twins, n. M. *aet.* 59, very short-sighted, indifferent health for 15 years, slow, rigid, dull, passive, ineffectual, fusser. (Abnormal personality, probably mentally retarded.) Sibs: 1. m. *aet.* 29, n. 2. f. *aet* 27, grammar school and teacher, n. 3. Twin. 4. Proband. 5. m. *aet.* 19, n. 6. f. *aet.* 15, n. All children left home immediately on completing schooling.

Two months premature; Twin 4½, Proband 4¾ pounds. Both breast-fed 3 months. Twin walked first, else development equal. Both right-handed. Both enuretic till 7, nail-biters, blinking tic, health-conscious. Both backward in all subjects, Proband slightly ahead, bottom of an A class, Twin bottom of a B class; both disciplinary problems. Both many changes of job, Proband the more and often out of work for minor illnesses. Both eventually found girl friends, but sex interest late and feeble. Health: both very short-sighted, many minor ailments; Proband "loves hospitals", daily on sick parade at detention centre; Twin numerous somatic complaints at Borstal, produced blood in his urine. Offences: Proband 3 times larceny; drunk and disorderly, misuse of phone and public nuisance (feigned he had been attacked); Twin 5 times larceny; false fire alarm, taking and driving away, twice arson. In personality Twin readier to fall in with a group, Proband more individualistic, yet Proband only joined local gangs. Twin did, Proband did not, maintain contact with family. Both very alike, lie and cover up for one another, noisy, untidy, irritable, destructive, a passion for knives and matches.

Both referred to C.G.C. at 7, "no treatment required". 1952 Twin referred to Children's Out-Patient Department, I.Q. 78, diagnosed "juvenile delinquency", home environment regarded as "non-traumatic", 60 therapeutic attendances; subsequently many delinquencies. 1959 seen again Maudsley Out-Patient Department by psychiatrist "hearing voices", plausible, evasive, unconvincing; later to Borstal. Proband attended Maudsley Out-Patient Department 23 July, 1957 for fits, sudden falling, no aura, no unconsciousness, etc. Has had attacks in which he had "seen" his father. I.Q. 75. Belle indifférence, shallow promises. Left leg found

slightly weak. On follow-up 1960, Proband is coping moderately, not self-supporting, often on Assistance, attends other psychiatric out-patient department. Twin at Borstal.

Conclusion: Differences between these mentally subnormal and psychopathic twins are quantitative and of minor degree; the more energetic Twin is a good deal more troublesome.

DZ 1 (b. 28.11.30). F. d. 58, cancer; unstable, bad tempered, heavy drinker, promiscuous, eventually deserted family (psychopath). M. *aet.* 64, n. Sibs: 1. f. *aet.* 41, n. 2. f. *aet.* 38, n. 3. m. *aet.* 37, grand mal attacks since 24 (epilepsy). 4. f. *aet.* 35, n. 5. Twin. 6. Proband.

Full term, difficulties—no details; Twin 4, Proband 3 pounds. Both breast-fed, Twin for 6, Proband for 15 months. Development equal. Both right-handed. Both temper tantrums, Proband worse—difficult, jealous, easily bored, quarrelsome. School: Proband a class behind, lazy, uninterested; at 12 Twin won place in technical school, took commercial subjects till 15. Both many jobs, Twin more stable record, Proband 28, unskilled jobs in 4 years and at age 20 on Disabled Persons Register. Menarche: Proband 11, Twin 12; both many boy friends but prefer making a foursome. Health: Proband slightly more minor illness. Twins very dependent on one another and in constant conflict with rest of family. Twin more placid, Proband excitable, unstable, violent tempered, lazy, idle, selfish, avoids helping in house.

Proband admitted Maudsley (in-patient) at 19 for 3½ months; ill for 3 years, fears of death, of enclosed spaces, very many somatic complaints, giddiness, faints, pains, breathlessness; shouts and screams in quarrels. EEG "mild paroxysmal dysrhythmia". Re-admitted 1957, *aet.* 26, for 6 weeks; similar symptoms, hypochondriacal, depressed, 6 E.C.T. without improvement. Twin attended Maudsley Out-Patient Department 10 December, 1954–8 March, 1955, *aet.* 24; depressed, loss of interest, poor appetite, difficulty getting off to sleep and early waking; worry over spots on skin. Diagnosed anxiety state and reactive depression. Treated by psychotherapy, discharged no change. Twin attended another hospital, recovered in 4 weeks after 5 E.C.T. Follow-up 1959, twins now only ones still living with mother. Twin has remained well, steadily at work, got engaged, but decided fiancé not the man for her a few days before wedding. Proband mopes at home, unable to work 1957–59, constantly complaining and discontented. Pressure headaches continue. 3 December before F.U. started office job. Is courting, reluctant Irish commercial traveller 5 years younger.

Proband is psychopathic in many ways, perhaps predominantly hysterical.

DZ 2 (b. 26.10.20). F. d. 80+, stroke, n., possibly slightly cyclothymic M. d. 62, cancer, liable to rages, mistreated F, constantly quarrelling (psychopath). Sibs: 1. f. d. 40, cancer, n. 2. m. disappeared to join Navy *aet.* 15. 3. m. missing presumed dead 30, n. 4. f. *aet.* 50, n. 5. f. *aet.* 48, erratic, excitable, sought limelight, n., hysterical personality. 6. m. *aet.* 36, n. 7. m. *aet.* 44, marked mood variations, n. 8. Twin. 9. Proband. 10. f. *aet.* 36, n. 11. m. *aet.* 34, reserved, shy, ? slightly obsessional, n.

The twins were 2 months premature, Proband's birth more difficult, breech; both blue and had to be revived. Twin 5½, Proband 5 pounds. Both bottle-fed. No difference in early development; Twin several times in hospital before 2 for operations on naevus. Twin right-handed, Proband left-handed. Proband more docile, fears of dark, etc., scared to do wrong; Twin nail-biter, but more sure of self. Proband 1 class ahead, A stream; Twin C. Proband scared of games, Twin tomboyish. Both domestic work till marriage; since marriages broke up, Twin cashier, Proband part-time waitress. Menarche both at 15. Twin liked boy friends, Proband scared and shy. Twin married 22, 2 sons; Proband 23, 4 pregnancies: 1. female died in infancy; 2. female hemiplegic, E.S.N.; 3. male attends C.G.C.; 4. terminated. Proband's husband left her 1950 for 3½ years. Health: Twin had chronic ear trouble as child and adult; Proband severe influenza at 7, with subsequent eye trouble and glasses; shingles at 12. Proband anxious obsessional worrier, perfectionist, socially retiring; Twin complete opposite, nothing worries her.

Proband after mother's death in 1943 complained of fears of falling, darkness coming over eyes; 1947 treated by psychotherapy, later by E.C.T. 1949 admitted (in-patient) Maudsley for 3½ months, tense, fidgety, weeping; EEG very unstable, metrazol produced burst of typical spike and wave; 40 psychotherapeutic sessions. 1950 obsessional fears of hurting child. 1951 depression, fear of harming children, in other hospital, E.C.T. improved. 1952 termination of pregnancy and sterilization, anxieties somewhat relieved; later more E.C.T. 1953 cortical undercut; 7 months later second operation, cut deepened; remained depressed, apathetic, black-outs. 1954 began to improve, family reunited. 1960 on follow-up no complaints, no fears, can go out, shop, etc., affect rather flat; unpredictable and rather irresponsible. Twin never under psychiatric care, but *aet.* 39 received treatment from family doctor with sedatives and tranquillizers; 1958 husband left her. 1960 on follow-up fairly well, at full-time work, divorcing husband.

Proband shows chronic primary tension state, much benefited by leucotomy.

DZ 3 (b. 9.5.22). F. *aet.* 74, quick tempered, n. M. *aet.* 75, n. Sibs: 1 m. *aet.* 56, n. 2. m. *aet.* 55, n. 3. m. *aet.* 54, n. 4. m. *aet.* 52, n. 5. m. *aet.* 50, n. 6. m. *aet.* 48, n. 7. f. *aet.* 46, n. 8. f. *aet.* 44, n. 9. Twin. 10. Proband. 11, 12. Twins. 11. f. *aet.* 36, n. 12. f. *aet.* 36, n.

No difficulties, Proband smaller and remained so. Development equal. Both right-handed. Proband lived with childless aunt between 2 and 4, much petted, well fed, well dressed; found

adjustment difficult on return. Neither neurotic traits. Both average at school till 14; Twin studious, a reader, Proband fonder of physical and social activity. Both trained as telephonist: Twin so employed in intervals of childbearing, Proband after psychiatric illness rose to senior secretarial position in charge of investment company office. Both married at 17, Twin to husband 5 years older, normal, 5 children; Proband to husband 10 years older, chronic nephritic, later impotent, no children. Health: despite urticaria better in Proband. Twin peritonitis, pyelitis, no allergy. Proband tense, efficient, driving, prone to mood changes, likes responsibility, few friends; Twin cheerful, easy-going, good contacts, liable to minor depression.

Proband admitted Belmont (in-patient) for 2½ months, *aet.* 28. For 2½ years tense, emotional, cries, heart pounding, stomach churns, feels distant and depersonalized, feels she is acting, marital worries; treated with psychotherapy. Follow-up 1960 now well, has had no recurrence, still many problems, still tense. Twin *aet.* 18 badly upset by air-raids; *aet.* 35 upset over pregnancy and advised to see psychiatrist ? termination, but improved with sedatives; six months after birth, depression, loss of appetite, insomnia; 1960 again depressed when pregnant, again recovered.

Proband's illness affective, anxiety-tension state largely environmentally determined: husband's prolonged and serious illness, financial problems and nursing elderly bed-ridden mother-in-law; twin liable to react to stress by depression.

DZ 4 (b. 21.9.14). F. d. pleurisy, 35, n. M. *aet.* 70+, irritable, possessive, worrying; *aet.* about 45, had nervous breakdown for 2 years, fits of depression, would wander round the house at night (menopausal depression). Sibs: 1. m. *aet.* 52, n. 2. f. *aet.* 50, possibly had depressive illness. 3. m. *aet.* 49, n. 4. f. *aet.* 45, n. 5. m. *aet.* 44, n. 6. Twin. 7. Proband.

Full term, no difficulties, both breast-fed, early development equal, Twin thought to be stronger, both right-handed. Twin, no nervous traits. Proband afraid of dark, sucked thumb, bit nails, food fads. Proband much brighter at school, also more conscientious and worrying, left from top standard at 14, where she had been 4 years. Twin from top standard at 13, where for 1 year. Twin many friends, Proband did not mix well. Twin hospital ward-maid till marriage at 22, Proband in grocery store before and after marriage, rose to manageress. Menarch Twin 11, easy, Proband at 17, periods always painful. Twin married 22, 2 children Proband 26, no children. Twin, no significant illness.

Proband nervous breakdown at 33, no treatment. Relapse at 36, multitudinous conversion symptoms, irritability, had had symptoms since childhood, never really adjusted, avoided difficult situations. In first hospital had 6 E.C.T. without benefit; after admission (in-patient) to Belmont, when 36 for 7 months, depressed, tense, agitated or unduly calm, histrionic, complaints of headache, fainting, memory lapses, fears, depersonalization, palpitations, loss of 3 stones weight. On follow-up 1958, since discharge has kept away from psychiatrists, G.P. gives sedatives, sleeping pills, frequent talks, no worse no better than 7 years ago; had had operations for hysterectomy (*aet.* 39) and hernia (*aet.* 41) physical symptoms related to operations. In interview, looks older than her years, sallow, wrinkled, expression in repose, pouting in discontent, affect shallow, tense, bored, unhappy. Husband is dominated by her symptoms. Twin flourishes.

Proband's symptoms are based on personality deviations existing from childhood.

DZ 5 (b. 5.1.17). F. d. by "old age", n. M. d. 65 "seizure", n. Sibs: 1. m. *aet.* 55, n. 2. f. *aet.* 52, n. 3. f. *aet.* 50, n. 4. m. *aet.* 47, n. 5. m. *aet.* 44, n. 6. Proband. 7. Twin. 8. f. aet. 38, n. 9. f. *aet.* 36, n. 10. f. *aet.* 33, n.

No information *re* birth, etc. Development equal. Equal average at school. Both stage dancers. Both married at 21, each 2 children. Twin, said to have been promiscuous, divorced and married again. Health: Proband operation for twisted ovary *aet.* 17, at 34 therapeutic abortion; Twin one minor gynaecological operation. Twin the more vigorous personality, very sociable, attractive to men, has had affairs; Proband more sensitive, reserved, prim. Proband refused to co-operate with investigation or allow us to see twin.

Proband attended Maudsley Out-Patient Department *aet.* 29, unreality feelings and somatic anxiety coming in attacks followed by headache and irritability. Recommended for psychotherapy, did not attend. *Aet.* 34 re-attended, out-patient department, headaches, irritability, two months pregnant. Recommended for psychotherapy, went elsewhere and pregnancy miscarried. 1958 follow-up, husband reports her well, regards her symptoms as no more than part of her personality.

Proband's symptoms appear to be very superficial manifestations of temporary discontents, based on personality deviations.

DZ 6 (b. 22.6.32). F. *aet.* 71, very conscientious and interfering, n. M. d. 66, stroke; anxious, n. Sibs: 1. Twin. 2. Proband.

Seven-months, artificial induction, no difficulties (Mother 40 when twins born); Twin 4, Proband 3½ pounds. Both weak babies; bottle-fed. Proband ahead in early development; Twin bronchial asthma. Twin right-handed, Proband left-handed. Twin asthma, severe till 11, occasional since. Proband at 13 had illness with jerky movements, provisional diagnosis "chorea", final diagnosis "habit spasm"; in hospital 4 months, not back at school till a year later. Proband was taller and stronger and ahead in development till then, afterwards was set

back; selfish, inconsiderate, difficult, obstinate, changeable, fears. Proband overshadowed at school, more fitful, less persevering, stayed on till 18 to train for librarian but failed exam. Twin steadily employed typist since 16; Proband one job as counterhand, left before 19 and has not worked since. Menarche: Proband 13, Twin 14. At 28 Twin is now engaged; Proband has never had any relationship with a man, in interview gives impression of homosexual potentialities. Twin much more social, though interests serious and much connected with local church; Proband never any friends.

Proband first admitted Belmont (in-patient) *aet.* 19, 25 September, 1951, for 10½ months; fear of blushing and of men; had a panic attack going home at night and fabricated story of having been attacked by a man. Panics continued, so father began meeting her. Proband soon unable to work, go out anywhere, eat, sleep. Father devoted his time to her, tried to organize her breathing, held her hand when she took her tablets or went to door for air. Out-patient psychotherapy failed. On admission tense, asthenic, jerky movements, gasping breathing. Discharged improved 9 August, 1952. Subsequent hospital admissions 26 May, 1953–5 November, 1955; 3 August, 1956–13 August, 1956; 13 February, 1957–14 August, 1958; 30 January, 1959–9 February, 1959; 6 March, 1959–13 March, 1959; 22 December, 1959–15 January, 1960. On follow-up, 1960, still under out-patient care, complains of intolerable tension, glib, histrionic, "too ill" to return to work or do any housework; interests: only reading novels, hospital attendances and relationship with therapist. Still taking large quantities of drugs.

Proband's long intractable illness appears to have begun as simple anxiety state but to have developed into an extreme dependence as result of over-permissive attitude towards her by others.

DZ 7 (b. 6.2.22). F. *aet.* 66, n. M. *aet.* 71, exaggeratedly invalided by rheumatism, irritable, n. Sibs: 1. Proband. 2. Twin. 3. f. *aet.* 36, epileptic from 9 to 14 (epilepsy).

Full term. difficulties, Proband instrumental; both about 6 pounds. Development equal. Both right-handed, Proband many neurotic traits, shy, serious; Twin lively, high spirited, normal. Proband better at school. Twin in shop or factory till birth of son, Proband many posts as clerk, etc., mostly held for fair periods. Menarche: Proband 11, Twin 16. Twin married a man soon killed in R.A.F., *aet.* 25 married again happily—2 sons. Proband had many inhibitions about marriage, at 33 found husband through marriage bureau, no children. Health: Twin obese and ? arthritic; Proband with menarche onset of atypical fits, ceasing with amenorrhoea of anorexia nervosa, recurring with return of periods after leucotomy. Repeated EEGs showed slow and fast dysrhythmia, nothing specific for epilepsy; clinical observation showed tetanic nature precipitated by overbreathing. 1960 fits continue 1 per month. Personality, Proband shy, reserved, conscientious from earliest years, Twin much more extraverted, sociable at very superficial level, vigorous, generous appetite.

Proband first admitted *aet.* 27 with severe anorexia nervosa, periods having ceased *aet.* 25, weight 6 stones 3 pounds: modified insulin, etc., no improvement, actively uncooperative; anterior leucotomy 18 July, 1950, improved, placid, gained weight, menstruation returned December, 1950. Fits then recurred, anti-convulsants ineffective. 1952 hysterical wrist-drop, then left hemiplegia, later hysterical gait; sullen, depressed, resistive; 8 E.C.T. ineffective. Admitted (in-patient) Belmont, March, 1953–June, 1954, psychotherapy, second leucotomy October, 1953, improved. Re-admission to first hospital January to March, 1956, grossly hysterical gait; modified insulin and chlorpromazine, gained 2 stones, gait persisted. 1960, follow-up, looks 10 years older than age, listless, affectless, rapid talk, gets up and down stairs on left knee and right foot; day completely filled with obsessional rituals, lists everything, all actions catalogued and timed, must count everything. Husband indulges her, frequently does all housework himself. Twin well.

Proband's illness is obscure; birth trauma, atypical epilepsy, eventual presenile dementia not easily excluded; husband has played a part in prolonging and promoting disability.

DZ 8 (b. 4.8.17). F. *aet.* 70, n. M. *aet.* 62, histrionic, voluble, aggressive, sentimental, selfish, n., hysterical personality. Sibs: 1. m. *aet.* 48, n. 2. m. *aet.* 40, n. 3, 4, 5. triplets. 3. Proband. 4. Twin, mentally retarded (mental defect). 5. f. d. infancy. 6. f. *aet.* 32, n. 7. m. *aet.* 30, n.

Full term, no difficulties. Proband ahead in development. Both right-handed. Proband no neurotic traits, but happy, generous, enthusiastic, liable to "crazes". Twin has always stayed at home. Proband trained as children's nurse, later S.R.N., ward sister, home sister, assistant matron. Never any love relationship of any kind. Proband happy, cheerful, generous, from childhood liable to enthusiasms, conscientious, energetic, obstinate; as sister in children's ward would spend up to £50 of own money on toys for children at Christmas; absolutely no sexual interests.

For history of illness, see text. Admitted Belmont (in-patient) 1953 for 4 months.

DZ 9 (b. 25.8.37). F. *aet.* 50, several times in mental hospital with hypomanic and depressive states (manic-depressive). M. *aet.* 56, she and father, children of DZ twin sisters;

aet. 52 attended Maudsley Out-Patient Department with anxiety-depressive state, diagnosed reactive, but she had previous illness at 17 and her father twice treated for depression (endogenous depression). Sibs: 1. Proband. 2. Twin. 3. f. *aet.* 13.

Full term, no difficulties; Proband 4 pounds 14 ounces, Twin 5 pounds. Breast-fed, Proband 10 weeks, Twin 9 months. Proband slightly behind in development and less strong. Proband ambidextrous, Twin right-handed. Proband thumb-sucker, nail-biter; *aet.* 12–14 treated for acidosis; pains and stiffness in legs, difficulties in walking, considered psychogenic (? rheumatism), 12–15 attended C.G.C. "anxious and self-dramatizing". From 11 to 20 severe dysmenorrhoea. Twin at 11 fits of violent rage, destructive, screaming, attacking mother and siblings; attended C.G.C. and again at 13 when depressed following jaundice. Both grammar school, O and A level passes, Proband arts, Twin science. Both to University, Proband English, Twin physics and electronics. Proband's 3rd year interrupted by illegitimate pregnancy. Menarche in both at 11, on same day, both much dysmenorrhoea. Both fell in love with 40-year old lodger ex-Rampton (pyromaniac), but Twin's attachment soon waned. Twin favours masculine dress, pursuits, hair style, manners, rides powerful motor-cycle, at ease with men if talking electronics, etc. Proband kept attachment to her criminal friend for 2 years visiting him after another offence had landed him again in prison. Parents felt it would have been "outrage to her loyalty" to object. Personality, Proband immature, bland, shallow, insincere, anxious, gushing, no friends outside family, intolerant, critical, striving for effect; Twin difficult, violent tempered at home, much better away, sensitive, immature, introverted, inclined to the masculine, but much more insight than Proband.

For history of illness, see text. Admitted Bethlem (in-patient) 1956 for 3 months. Attends Maudsley Out-Patient Department for 1 year. Re-attends Maudsley Out-Patient Department 1958 for 1 month.

Illness of Proband probably cyclothymic.

DZ 10 (b. 22.5.32). F. *aet.* 63, quick tempered, n. M. *aet.* 58, had gall-stones; was irritable and depressed and made family miserable for 1 year until operation (reactive depression). First 3 siblings died in succession *aet.* 3. 4. f. *aet.* 38, n. 5. f. *aet.* 36, n. 6. f. *aet.* 34, n. 7. m. *aet.* 32, n. 8. Proband. 9. Twin. 10. f. *aet.* 26, n. 11. m. *aet.* 24, n. 12. m. d. 2.

No birth difficulties. Twin always bigger and stronger and a little ahead in development. Proband timid and shy as child. Both had poor education, Proband behind Twin. Twin started work *aet.* 13 in factory and later a variety of other unskilled jobs, leaving when pregnant. Proband started as domestic at 14, later in factory and office jobs, with one firm for 8 years till marriage; returned to work when baby died leaving when again pregnant. Twin married at 18 a packer, has had 6 pregnancies, including miscarriage of twins. Proband married at 20 a machine operator, 2 pregnancies, some marital difficulties. Physical health: Twin good, Proband in hospital 4 times with septic leg, confinements, gynaecological operation. Twin, sturdy, vigorous, slapdash and slovenly, never worries. Proband always shy, food fads; but at F.U. shows herself brisk, competent, actively sociable, somewhat perfectionist, affect tepid.

Proband attended Maudsley Out-Patient Department once only *aet.* 24, complained of blackouts, headaches, depression; had been seen by G.P. after 2 fits, semiconscious, disoriented, having bitten tongue. Hospital investigation negative. Seen by psychiatrist, domestic difficulties disclosed, fits regarded as almost certainly hysterical. On F.U. 1960 describes symptoms of past illness as coming on after death of first baby at birth, depression, loss of interest, initiative, appetite and weight, headaches, insomnia, tension, irritability; had improved slowly, and got well after being reunited with husband in Council flat. 1960, Twin well.

Proband's illness mysterious, with possibilities of epilepsy and of endogenous depression.

DZ 11 (b. 20.2.26). F. *aet.* 60, drinks, n. M. *aet.* 58, short-tempered, drinks, n. Sibs: 1. Twin. 2. Proband. 3. m. *aet.* 32, n. 4. m. *aet.* 23, liable to headaches, attempted rape (criminal psychopath), 5. f. *aet.* 19, n.

Full term, no difficulties, Twin 7½, Proband 6½ pounds. Later twin smaller. Proband nail biter. Equal achievements at school, left 14 without exams. Proband steady worker in mines, Twin work-shy, miner when working, for years on Assistance, has been in prison for shop-breaking. Twin not known to have had any relationship with a woman, lives with family. Proband married 30, no children. Twin no important illness. Proband bronchitis, anaemia, pneumonia and pleurisy four times 20–27; occupational accident. Personality, Twin little known, never liked work; Proband quiet, few friends, moods of depression, *aet.* 24–25 heavy drinker.

Proband *aet.* 26 wandered from home, found self 20 miles from home 4 days later. *Aet.* 27 industrial accident, tore muscles of right arm, compensated and job guaranteed. *Aet.* 30 married, on honeymoon money ran out, wandered off, found one week later. *Aet.* 32 another fugue when on point of taking test for promotion to mining deputy. Found 1 week later in London. Admitted then (1958) Maudsley (in-patient) for 7 weeks. Unwilling witness, dull, apathetic, disinterested. Discharged to out-patient supervision at local hospital. On F.U., 1960, Proband working, no longer under care. Twin well.

Hysterical symptoms based on personality much liable to dissociation.

DZ 12 (b. 8.11.18). F. d. 76, thrombosis, n. M. *aet.* 72, all her life malade imaginaire, mplaining of heart, uses symptoms in moral blackmail (abnormal hysterical personality). bs: 1. f. *aet.* 45, n. 2. Proband. 3. Twin.

Full term, no difficulties, Proband 3½, Twin 6½ pounds. Throughout infancy Proband naller, more delicate, had pneumonia, tonsils, etc. Development equal. Proband occasional ints, all life nail-biter, afraid of dark, difficulties in coping with tension; Twin afraid of ark as child, nail-biter till 30s, tense. Both grammar school (fee-paying) till 17; Twin a ass ahead in all subjects. Both typists with steady record till marriage and first babies. Menarche Twin 15, Proband 16; mother prudish, no information, Proband very upset, periods anty, dysmenorrhoea till first baby born. Twin's marriage normal; m. DZ twins. roband married unsociable, rigid vegetarian and valetudinarian, never at ease with him, sons. Personality, Proband a worrier, painstaking, energetic, tense, insecure, throws herself to strenuous activity, best in situations of crisis (as when serving with Free French during ar), minor obsessional traits, very active socially; Twin more poised and easy, extravagant, ccasionally depressed and irritable.

Proband noted increasing libido from January, 1957. Early July, 1958 family doctor lled at midnight on account of a "stroke" found her with left hemiparesis and left extensor lantar response. Attended Maudsley Out-Patient Department 14 July, 1958, excited and gitated, having in past weeks indulged in sex play with an older married man; he had imulated her much more than her own sexually uninterested husband could ever do. Guilt nd agitation unrelieved by measures advised (e.g., confession to husband). Intense lasting exual excitement and spontaneous orgasms led to admission to National Hospital, treatment y tranquillizers and E.C.T. Went home less depressed, still tense. 1960 follow-up, still xtremely tense, very high libido inadequately controlled by masturbation. Twin well.

Proband's illness is quite obscure but its nature strongly suggests a physical basis. Nothing ysterical was observed at the National Hospital.

OBSESSIONAL ILLNESS IN MENTAL HOSPITAL PATIENTS

By

I. M. INGRAM, M.D., D.P.M.

Lecturer in Psychological Medicine
University of Glasgow

Introduction

The descriptive study reported here has three main objects: to describe in detail the natural history of a group of obsessional patients; to compare the findings in this group with those in comparable groups of hysterics and anxiety neurotics; and to find in what ways a sample composed of in-patients of a mental hospital differs from other groups of obsessional patients previously described.

Comprehensive studies of large numbers of obsessionals are few. The only ones which deal in any detail with the natural history of the illness are by Lewis (15), Müller (17), Rüdin (25) and Pollitt (21), although many other writers deal with details of the subject. As it will be necessary to refer to the work of these authors frequently, the types of case they studied and the length of follow-up will be stated briefly. Lewis followed up 50 cases of obsessional illness, both out- and in-patients, over five years, discussing course, outcome and family history. Müller was able to contact 57 out of 84 patients after as long as 20–30 years in most cases. As the average age at follow-up was 55, this is the longest follow-up and the best guide to the effect of ageing on the obsessional state. Rüdin's series is the most detailed and comprehensive, comprising 130 patients, the majority in-patients. They were cases of obsessional illness in a broad sense, and included 25 doubtfully psychotic cases and 13 cases first diagnosed as obsessional who became psychotic. Genetic factors are emphasized but the natural history is also considered in detail. Pollitt followed up 150 cases, 69 of whom were in-patients and 81 out-patients seen in private practice. Only obsessional neurotics were included and all doubtful or borderline cases were excluded. The natural history was investigated and the average duration of follow-up was 3·4 years.

There is general agreement among the quoted authors on the definition of obsession. That usually accepted is by Schneider (27) who stated that an obsession exists whenever a person cannot exclude thoughts from consciousness, distinguishes them as unreasonable or without basis, but is mastered by them. Lewis (15) lays more stress on the subjective feeling of resistance than on the recognition of senselessness, but both are implicit in Schneider's definition which is used in this work. There is less agreement on the use of such terms as "obsessional illness", "obsessional neurosis" and "obsessional state". Throughout this paper "obsessional illness" will be used to designate the wide range of patients whose symptoms are predominantly obsessional. The term "obsessional neurosis" will be used to describe the most typical cases of obsessional illness, excluding any cases in which schizophrenia, depressive illness, or organic illness is suspected.

Diagnostically these studies can be divided into those which deal with obsessional neurosis and those which deal with obsessional illness. Lewis and

Pollitt are concerned with "pure" cases of obsessional neurosis and exclude doubtful and atypical cases, while those of Rüdin and Müller cast a wider net and deal with obsessional illness. These differences in diagnostic criteria add to the difficulties in comparison but all these authors make their methods of diagnosis explicit. In many other sources no clear statements on diagnosis are made.

There are other differences in selection. When groups contain different proportions of out-patients and in-patients the severity of the cases may differ. It would be expected that different proportions of paying and non-paying patients would also have an effect on results. Only when these differences are made explicit can comparisons be profitable.

Control groups are necessary. Data on precipitants, childhood symptoms, and many other matters cannot be evaluated unless results collected in a similar way are available for normal subjects or other neurotics. Many authors do not provide such information.

It is hardly surprising that many simple problems are unsolved and that major contradictions can be found in comparing results. The most obvious and urgent problems concern the course and prognosis of obsessional states. When opinions on natural history diverge the evaluation of treatment, particularly leucotomy, is inordinately difficult. The present investigation was planned to investigate these problems and avoid some of the criticisms. It differs from previous work in considering mental hospital in-patients only, and in providing comparative data for other neurotic groups.

Admission to hospital ensures that the cases are of some severity and that a reliable picture of the natural course of severe cases will emerge. In hospital a detailed record of the individual's day-to-day behaviour can be made and more detailed case-taking is possible than in most out-patient clinics. Many in-patients have been ill for years prior to admission and the course of the illness can be studied retrospectively as well as by follow-up. In hospital cases the possible relations with and development of psychotic states is more obvious. Against these advantages there is the objection that an in-patient sample is likely to contain more chronic and severe cases and will give a biased view of prognosis and of the results of therapy. For prognosis, the objection is valid; but it does not apply to therapy, for the results in severe cases provide a useful basis for assessing the results of treatment in severe cases. In particular, the results of leucotomy can be compared with the results in patients who were not offered or refused the operation. It can be said that severe obsessional neurotics may differ in other ways as yet unknown from a sample of both out-patients and in-patients. This objection can be turned to good account by comparing the results with those obtained in "mixed" populations and considering in what way the present group is similar and in what way dissimilar. The advantages to be gained from studying a homogeneous sample compensate for the few disadvantages.

The gathering of similar data for groups of hysterics and anxiety neurotics makes it possible to compare the obsessional patients with other hospitalized neurotics. In psychological research Eysenck has aligned the obsessional and the anxiety neurotic in his dysthymia concept (4, 5). Other psychological research casts doubt on the validity of this grouping (9, 10) but there is a dearth of clinical information on the subject.

Method and Classification

The group comprised 89 patients admitted to Crichton Royal, Dumfries, in the years 1946–1956 who were classified as suffering from obsessional states.

Since mild obsessional illness rarely merits admission to hospital, since no out-patients were considered, and since phobic anxiety cases were classified under anxiety reactions, the group was presumed initially to be a sample of serious cases with predominantly obsessional symptoms. Detailed case records were available for these patients and all admitted during the last three years of the period had been examined personally, while many of the earlier cases were examined during the follow-up. All cases which presented diagnostic difficulty had been discussed at staff meetings and conclusions noted. It was possible to obtain information for all cases on a wide variety of details. The only order imposed on the material as a whole was the division of the cases into the five categories named and defined below. These diagnostic subdivisions were in all cases expressed by the original psychiatrists, implicit in their comments and formulations, or elucidated in discussion with them.

The categories used were:

1. *Obsessive-compulsive Neurosis*

A classical or nuclear group, justifying the description of typical obsessional neurosis: obsessional and compulsive symptoms giving rise to a sustained symptom complex with no question of psychotic disturbance of thought or mood, organic nervous illness or other neurotic symptoms. Any cases in any way atypical were automatically and strictly excluded from this group.

2. *Phobic-ruminative States*

This category was used for those cases with predominantly phobic and ruminative symptoms, with minimal or absent motor symptoms and no psychotic or organic signs.

3. *Doubtfully Schizophrenic*

It was anticipated that this would be a useful category in an in-patient group and its use had a precedent in Rüdin's work. It consists of those cases in which symptoms suggestive of schizophrenia were found and in which there was a measure of disagreement regarding the differential diagnosis among the medical staff although the final classification was as an obsessional state. The most common difficulties were doubt about the resistance to his symptoms felt by the patient or about recognition of their absurdity. It was presumed that this group would contain any patients found to be schizophrenic at follow-up.

4. *With Depressive Features*

This group contained those patients showing sustained depressive symptoms. The category was designed to explore the borderland between obsessional neurosis with depressive features and endogenous depression with obsessional symptoms—the "endogenous obsessional neurosis" of Mayer-Gross *et al.* (16). In addition to mood, such factors as early waking, diurnal variations in symptoms, and obsessions with a depressive content were considered in selecting patients for this group.

5. *Miscellaneous*

Those patients who, while having predominantly obsessional symptoms, could not be included in the other groups because of other atypical features.

These clinical divisions were made on the basis of the total impression of the patient and before the detailed descriptive data were transferred to cards for analysis.

For most findings data for patients suffering from anxiety neurosis and hysteria are also presented. One hundred consecutive discharges classified as hysteria and another hundred classified as anxiety neurosis were taken and their case records examined. Both series commenced in 1951; the date was selected as the mid-point of the period covered by the obsessional cases. Because anxiety neurosis and hysteria are of high incidence a consecutive series was considered the best way of obtaining an unbiased sample. The same technique was used for collecting and assessing data in both the obsessional and control groups.

General Findings

Diagnosis

The division of patients among the diagnostic categories defined above was as follows:

	Number	*Percentage*
1. Obsessive-compulsive	37	42
2. Phobic-ruminative	16	18
3. Doubtfully schizophrenic	14	15·5
4. With depressive features	10	11
5. Miscellaneous	12	13·5
	89	100

Difficulty in allotting a patient to one of the above categories was rare. Had it not been for the question-begging nature of the doubtfully schizophrenic category many more problems would have arisen as the most common one was the differential diagnosis between obsessional illness and schizophrenia. The provision of a miscellaneous category was also helpful in dealing with atypical cases.

In the phobic-ruminative group it was possible to distinguish clearly between ruminative and phobic anxiety states. Of the 16 cases, six showed severe phobic anxiety states distinguished by their recent onset, marked anxiety, minimal ruminations and rapid recovery. Six cases showed a ruminative state with few other obsessional symptoms and an absence of overt anxiety which together with their longer course distinguished them from the phobic states. Only in four cases was there diagnostic difficulty. Two of these showed a mixed phobic and ruminative picture with moderate anxiety, and could not be allotted easily to one or other category although they were nearer to obsessional illness than to anxiety neurosis. In the other two cases ruminations predominated but some motor symptoms with related phobias were present and they were felt to be on the dividing line between this and the obsessive-compulsive group. As ruminations predominated they were placed in this group.

No quantitative value relative to the other groups is placed on Group 2 as a whole; a few of the cases might properly be classified as anxiety states. This consideration does not apply to the purely ruminative states which are unlikely to be misclassified. Their number in the group probably gives a good estimate of their incidence relative to obsessional compulsive neurosis in the hospital population, i.e., 7 : 37.

In the miscellaneous group the 12 patients comprised three cases associated with organic nervous disease; three cases considered to be severe obsessional personalities (one with an anxiety state, one with reactive depression and the third with a mild drug addiction); five cases showed definite hysterical symptoms and hysterical personality traits; and one patient showed aggressive psychopathic symptoms.

Incidence

The 89 patients represent 0·88 per cent. of all admissions to the hospital during the period and 0·99 per cent. of voluntary admissions. Table I shows other figures that have been traced.

TABLE I

Incidence of Obsessional Illness in Hospital and Out-Patient Clinics

Series	Out-Patients		In-Patients	
	Number	Incidence (Per cent.)	Number	Incidence (Per cent).
Blacker and Gore (2) ..	226	2·9	99	3·1
Pollitt (21)	81	<2	69	<4
Registrar General (22) ..	—	—	375	0·7
Ross and Rice (24)	5	0·25	7	0·2
Slater (28)	—	—	20	1·0
Eysenck (4)	—	—	146	2·0
Present series	—	—	89	0·9

Obsessional patients are rare in both out- and in-patient practice, the number of out-patients never exceeding 3 per cent. and the number of in-patients usually being less and varying with the type of hospital. The Registrar General's low figure for mental hospitals in England (0·7 per cent.) when expressed as a percentage of neurotics admitted is still only 4·6 per cent. Those of Ross and Rice (24), relating to a naval hospital in wartime, are low although their figure for officers, both in-patient and out-patient, is higher (1·6 per cent.).

The incidence of 0·9 per cent. in this mental hospital population approximates to the Registrar General's 0·7 per cent. for all mental hospitals in England and Slater's 1 per cent. for a largely neurotic in-patient group in wartime. The higher figures of 3·1 per cent. at the Maudsley Hospital (2) and 4 per cent. at St. George's Hospital (21) are probably due to differences in selection of patients for admission (for example, for teaching purposes or leucotomy) but a higher incidence in urban districts is another possible explanation.

From the evidence available obsessional states are rare in psychiatric practice, whether in war or in peace, in hospital or in clinic. This does not mean that the true incidence in the population is necessarily low. Stengel (31) has stressed the secrecy of the obsessional patient and it will be shown that these patients are slower than other neurotics to seek help. It is likely that many obsessional neurotics deal with their symptoms as best they can without psychiatric help.

Sex Incidence

The group contained 34 men and 55 women (female=62 per cent.). The obsessive-compulsive group comprised 10 men and 27 women (female=73 per

cent.). The other subgroupings followed the general trend with the exception of the doubtfully schizophrenic patients, 10 of whom were men and only four women.

In the control groups there was also an excess of women: 66 per cent. in the anxiety neurosis group, 80 per cent. in the hysteria group.

The number of women suffering from hysteria is significantly higher than the number in the obsessional group ($\chi^2=17\cdot1$, $P=<0\cdot01$) but the obsessionals do not differ significantly from the anxiety neurotics, nor do the two control series differ significantly.

This excess of women in each of the groups is due largely to a higher number of female beds allowing a quicker turn-over.

Table II contrasts the above findings with those in previous series.

TABLE II

Sex Incidence in Groups of Obsessional Patients

	Pollitt (21)	Registrar General (22)	Rüdin (25)	Müller (17)	Blacker and Gore (2)	Present Series
Male	63	181	55	37	129	34
Female	87	194	75	20	119	55
Female (per cent.)	58	52	58	35	48	62

The average of these series is 52 per cent. female. The larger the group the nearer does the sex ratio approach unity. Pollitt's figures and the present ones are biased by the fact that more female beds were available for in-patients. On the available evidence there is no reason to suppose that women are more disposed to obsessional disorders than men.

Marital Status

Of the 34 men 23 were single (68 per cent.), and of the 55 women 22 were single (40 per cent.), giving figures for the whole group of 44 married and 45 single—a celibacy rate of 51 per cent. Of the 100 hysterics 48 were single and of the 100 anxiety neurotics 27 were single.

More of the obsessional patients than the anxiety neurotics are single ($\chi^2=19\cdot7$, $P=<0\cdot01$) but the celibacy rate does not differ significantly between the obsessional and hysterical groups.

Only two other figures are available for celibacy but they are both from relatively large series—47·7 per cent. of Rüdin's 130 and 52·7 per cent. of the men, 37 per cent. of the women in the Maudsley Statistical Report for 1949–51. In the latter series more men are single than in other neurotic disorders but the celibacy rates are lower than those found in schizophrenia (75 per cent. males, 58 per cent. females).

The high rate of celibacy accords with these previous observations. The figure for men is especially high. That nine of the 10 men in the nuclear group were single reflects the social incapacity caused by severe obsessional illness. The anxiety neurotics are less celibate than the hysterics and the obsessionals, probably because their illness shows less tendency to chronicity.

Fertility

Expressed as number of children per marriage, the fertility rate for the men was 1·1, for the women 1·1. The total fertility rate of 1·1 compares with

1·5 for the 100 anxiety neurotics and 1·5 for the 100 hysterics, calculated in the same way. No correction for duration of marriage having been made, the figures cannot be compared with the general population statistics of the Registrar General.

Fertility rates expressed as children born alive per marriage are available for two previous series: Rüdin 1·7, Blacker and Gore, males 1·6, females 1·3. Again the rates cannot be compared with those available for the general population but they are surprisingly low compared with Kalman's figure of 1·9 for institutionalized schizophrenics (13).

In the Maudsley Statistical Report there is no difference in fertility between obsessionals, anxiety states, hysterics and schizophrenics: here the obsessional patients are less fertile.

The figures for fertility are low in comparison with the previous series and the control groups. Unlike celibacy this cannot be attributed to social incapacity and it does not seem unduly speculative to connect this finding with a dislike or rejection of sexual matters in these patients, which would apply equally to men and women and to all the diagnostic subgroups, no differences between them being apparent.

Social Class

It was impossible to measure social status accurately by the conventional method of using occupation or husband's occupation. In the case of the female patients the data on the husband's occupation was often too imprecise to be a useful indicator of social status. The method finally adopted was comparison of the proportions of amenity bed patients (Sections 4 and 5) and non-paying patients (Section 3). This division probably correlates with social class fairly highly but does not permit direct comparison with other work.

TABLE III

Proportions of Paying and Non-Paying Patients in Different Diagnostic Categories—Expressed as Percentages

	All Patients	Obsessionals	Anxiety Neurosis	Hysteria
Non-paying	42	17	28	38
Paying	58	83	72	62
No. of patients	5,500	89	100	100

The obsessional group does not differ from the anxiety neurotics, but contains more paying patients than the hysteric group ($\chi^2=17·9$, $P=<0·01$).

Janet (12) found that his psychasthenic patients were more common in private than in hospital practice and suggested that a certain degree of "culture intellectuelle" plays a role in the development of the illness. Subsequent work confirms this observation, although it is difficult to separate the effects of social class from those of intelligence. Rüdin investigated social class and found it to be significantly above average in obsessionals and in their parents, siblings and children. Ross and Rice report a higher incidence in naval officers compared with ratings, and Slater found a higher number of non-commissioned officers among obsessional patients than among other neurotics.

The indirect method of class assessment used here shows that the obsessional patients are of higher social class than other hospital admissions.

Intelligence

Scores on Raven's Matrices and the Mill Hill Vocabulary Test were available for 76 of the obsessional group, 97 anxiety neurotics and 95 hysterics. The results of both tests are expressed as percentile grades: Grade 1=95th percentile and over, Grade 2=75th to 95th percentile, Grade 3=25th to 75th, Grade 4=5th to 25th, and Grade 5 the 5th percentile and under.

The results of the tests are shown in Tables IV and V.

Table IV

Percentile Matrices Grade for Obsessional and Control Groups

	Grade 1	2	3	4	5	Total
Anxiety neurosis ..	11	26	34	17	9	97
Hysteria	9	23	32	18	13	95
Obsessionals	14	25	26	6	5	76

Table V

Percentile Grades for Mill Hill Vocabulary for Obsessional and Control Groups

	Grade 1	2	3	4	5	Total
Anxiety neurosis ..	9	18	52	17	1	97
Hysteria	5	20	46	24	0	95
Obsessionals	10	24	37	5	0	76

For statistical calculation the results were condensed into those above average (1 and 2), average (3) and below average (4 and 5). The results were then expressed as percentages, χ^2 tests done, and the χ^2 in each case corrected both by Yates' method and for size of sample.

The results are as follows:

Matrices

1. Anxiety Group and Obsessional Group — $\chi^2 = 6{\cdot}7$, df=2, P=<0·05
2. Hysteric Group and Obsessional Group — $\chi^2 = 14{\cdot}6$, df=2, P=<0·01
3. Anxiety Group and Hysteric Group — $\chi^2 = 1{\cdot}32$, df=2, P=not significant

Vocabulary

1. Anxiety Group and Obsessional Group — $\chi^2 = 15{\cdot}6$, df=2, P=<0·01
2. Hysteric Group and Obsessional Group — $\chi^2 = 18{\cdot}7$, df=2, P=<0·01
3. Anxiety Group and Hysteric Group — $\chi^2 = 1{\cdot}75$, df=2, P=not significant

These results show that on both verbal and non-verbal tests of intelligence the obsessional patients score more highly than the other neurotics at a high level of significance.

The clinical observation that obsessionals tend to be of high intelligence was made by Kraepelin (14) and subsequently repeated by many authors. In Rüdin's 130 patients both intelligence and school record were higher than in a control group and Greenacre (8) noted that between a quarter and a third of her 86 patients were of college or professional educational status while only five patients could be considered dull.

The problem of intelligence in neurosis was fully investigated and reviewed by Eysenck (3, 4). He found neurotics to score slightly below normals in Raven's

Matrices but mentioned that in civilian populations neurotics have often been found to be more intelligent than normals. Analysing his results in terms of the hysteric-dysthymic dichotomy he found that in terms of intelligence hysterics are more frequent among the lowest 10 per cent. of the population while dysthymics are more frequent in the highest 10 per cent. He suggested that although the difference was significant it merely indicated a trend. He found that on vocabulary tests dysthymics have a good vocabulary relative to their intelligence whereas hysterics are markedly inferior on vocabulary (see also Himmelweit, 11).

For the present purpose Eysenck's dysthymic group is an unhelpful one, obsessionals in small numbers being grouped with large numbers of anxiety states and reactive depressions. In a study comparing equal numbers of obsessional neurotics, anxiety states and hysterics on Raven's Matrices, Cattell 2A and 2B and the Shipley Vocabulary, Slater (29) found that the obsessionals had significantly higher Matrices and Cattell scores than any of the other groups and significantly higher vocabulary scores. In addition, the other groups did not differ among themselves. These findings are in exact agreement with the present results and confirm in one respect the over-simplification of the dysthymia-hysteria concept.

It is difficult to explain this consistent finding in obsessional patients and to separate social class and intelligence, although the latter seems the most important. Whether the link is a genetic one, or whether leisure or training and practice in abstract thinking predispose to rumination and obsession is uncertain. In those patients of very low intelligence the symptoms tended to be less structured and less abstract and typically complicated rituals were less often seen. The total picture in these cases was fragmented, with isolated unconnected and unsystematized obsessional symptoms which the patient found difficult to describe.

Course of the Illness

Onset

(a) *Childhood Symptoms*

Neurotic symptoms in childhood were common enough to warrant separate analysis. Childhood was defined as under 14 years, and since almost all children show ritual behaviour and mild phobic symptoms at some period of development care was taken to exclude cases in which they could be considered within the normal range. The classification used for other childhood symptoms is evident in Table VI.

Table VI

Neurotic Symptoms in Childhood

Symptoms	Obsessionals (89)	Anxiety Neurotics (100)	Hysterics (100)
Phobias	8	2	2
Phobias and rituals	14*	–	–
Stammer	4	2	1
Psychosomatic illness	3	1	1
Conversion symptoms	–	2	5
Enuresis	1	3	5
Nightmares, terrors	1	5	3
Others	1	3	2
Total	32 (36%)	18	19

* Nine showed rituals alone, four phobias and rituals and one phobias, rituals and ruminations.

Thus 22 (25 per cent.) of the obsessional group showed obsessional symptoms in childhood compared with 2 per cent. of the other neurotics, while 36 per cent. showed neurotic symptoms before 14, twice as many as in the control groups.

The frequency of childhood symptoms has been noted by others. Those of Pollitt's patients with a history of previous attacks showed a peak incidence at age 11 to 15, while 35 per cent. of Rüdin's patients had symptoms before 15 years. Of the 86 patients of Greenacre, 64 had a history of ritual behaviour before puberty but only one of 30 normal controls denied similar symptoms in childhood. It is probable that in these cases ritual activity without subjective resistance, and therefore not truly obsessional, is being described. That this is so is suggested by the work of Berman (1) who found 62 children showing obsessional phenomena in the broadest sense (including "impulsions" or unresisted symptoms) but considered only four of them to be suffering from a true obsessional neurosis. The same author, following six cases of childhood obsessional neurosis to late adolescence, found two to be probably schizophrenic, two to be developing a severe chronic obsessional state and two to be well, having suffered only a short benign episode. Unfortunately no prospective studies over a longer period are available for children.

In the present group the findings, that childhood symptoms are twice as common as in other neurotics and more closely resemble adult symptoms, suggest that the obsessional tendency as distinct from neuroticism is of early onset and must either be genetically determined or stem from early experiences.

(b) *Precipitants*

Precipitants were defined as events occurring within one year of the onset of the illness which were considered both by the patient and the doctor to be related to the onset of symptoms. For example, "adolescence" as a precipitant implies both that the physical phenomena of adolescence coincided with the onset and that these phenomena concerned the patient or were evident in the symptom content.

TABLE VII

Precipitants of Illness

	Obsessionals (89)	Anxiety Neurosis (100)	Hysterics (90)
Physiological:			
Pregnancy	15	6	3
Physical illness	11	9	11
Adolescence	5	0	2
Menopause	2	2	2
Total	33	17	18
Psychological:			
Sexual and marital difficulties	12	15	6
Illness or death of near relative	11	14	9
Total	23	29	15
Others	6	4	9
None obvious	27	50	58

Precipitants are significant in 62 (69 per cent.) of the obsessional group, compared with 50 of the anxiety neurotics and 42 of the hysterics. The total of precipitants in Table VII does not correspond with the number of cases because of the presence of more than one kind of precipitant in several individuals.

In the obsessive-compulsive group precipitants were important in 29 cases—78 per cent. of the group. Physiological precipitants numbered 17, psychological 8 and others 4. Of the physiological precipitants pregnancy made up nine cases, that is, one-third of the 27 women in the group.

In the cases following childbirth (27 per cent. of all the women) a similar pattern of symptoms was seen: fears of harming the child, and washing and avoidance rituals involving both child and mother being almost always present. There is no previous record of such findings. It may be that these cases are more readily admitted to hospital because of the effect of the illness on the child but this does not explain the difference in incidence from the control groups.

The importance of precipitating factors was considered by Rüdin and Pollitt. Rüdin found them to be important in 75 of 130 cases, 24 occurring in childhood, 22 in adult life and 29 in both periods. Pollitt classified the precipitating factors in 93 cases and, comparing them with those in a series of non-obsessional admissions, found a preponderance of sexual precipitating factors in the obsessional patients. "Death of a near relative" was also a more frequent precipitant in the obsessional cases. It is of interest that Rüdin who proposes a genetic theory of aetiology stresses the importance of precipitants.

Precipitants are more common in this than in Rüdin's series, despite a more rigid time criterion for their definition. The results do not confirm Pollitt's finding that sexual factors and illness or deaths among relatives were more frequent in an obsessional group than in other admissions. With neurotics alone as controls there is little difference in respect of these items.

The positive findings are that precipitants are more commonly present than in the control groups; that they are more common in the compulsive group; that both physiological and psychological precipitants are found more often; and that the most common precipitants are pregnancy and childbirth. The highest incidence was among 19 married women in the compulsive group in whom the illness was precipitated by pregnancy or childbirth in nine cases. This high incidence is not found in the control groups.

(c) *Age of Onset*

TABLE VIII

Age of Onset

Age Group	0–14	15–24	25–34	35–44	45–54	55–64	65+	Total
Obsessionals ..	13	43	21	5	4	3	0	89
Anxiety states ..	2	36	30	22	9	1	0	100
Hysterics	0	24	44	20	10	2	0	100

Obsessional group: Mean=24·7 SD 11·5 (obsessive-compulsive group mean =22·9 years)
Anxiety group: Mean=32·2 SD 9·8
Hysteric group: Mean=30·3 SD 10·5
Obsessionals and Anxiety Neurotics: $t=4\cdot8$ $P<0\cdot01$
Obsessional and Hysterics: $t=3\cdot5$ $P<0\cdot01$
Anxiety Neurotics and Hysterics: $t=1\cdot3$ Not significant

The age of onset in the obsessional group is earlier than in the controls by some 5 years.

Fifteen per cent. of the obsessional patients have symptoms before the age of 15, 63 per cent. before 25, 87 per cent. before 35 and 92 per cent. before 45. Of those in the pure obsessive-compulsive group 11 per cent. have symptoms before 15, 70 per cent. before 25 and 94 per cent. before 35.

Obsessional symptoms begin at an early age. Of Rüdin's patients, symptoms began before the age of 20 in 47 per cent., before 30 in 81 per cent. and before 40 in 88 per cent. Pollitt found the average onset of symptoms to be 20 years for men and 22 for women, with 68 per cent. having symptoms before 25 years and 97 per cent. before 45. Greenacre found that acute symptoms begin most frequently between 21 and 25 years but that two-thirds of patients give a history of earlier milder disturbances.

The present results are very similar. The younger age of onset compared with other neurotics is in accord with the higher incidence of childhood symptoms.

Age of Admission

Table IX

Age on First Admission to Hospital

Age in Years	15–24	25–34	35–44	45–54	55–64	65+	Total
Obsessionals ..	15	36	14	14	8	2	89
Anxiety neurosis	5	30	29	17	14	5	100
Hysteria	18	25	25	21	7	4	100

Obsessional group:	Mean=36·1 years	SD=11·6 (nuclear group mean=34·8)
Anxiety Neurosis group:	Mean=41·0 years	SD=11·3
Hysteria group:	Mean=38·6 years	SD=13·4
Obsessionals and Anxiety Neurosis:	t=2·9	P<0·01
Obsessionals and Hysteria:	t=1·4	Not significant
Anxiety Neurosis and Hysteria:	t=1·3	Not significant

The obsessionals are admitted to hospital at a younger age than the anxiety neurotics but do not differ from hysterics in this respect.

Onset-Admission

Forty-eight (54 per cent.) of the obsessional group are not admitted until five years after the onset of the illness compared with 37 per cent. of the anxiety neurotics and 32 per cent. of the hysterics. Twenty-seven (33 per cent.) are not admitted until 15 years after the onset compared with 10 per cent. of the anxiety neurotics and 12 per cent. of the hysterics.

Despite the early onset the obsessional patient is neither admitted to hospital early nor seen earlier as an out-patient. In post-war figures for the Maudsley Hospital (2) the average age on admission was 33·2 years for men and 34·7 for women. Rüdin noted that 48 per cent. were admitted before 30 and 65 per cent. before 40. In the latter's patients the average duration from onset of illness to incapacity was 4·7 years, but there were wide variations. The long period intervening between onset and seeking advice reflects the secrecy and self-blame of the obsessional patient.

Type of Course

Four types of course were distinguished:

1. Constant, worsening: in which the illness had run an unremitting course with definite worsening—35 cases (39 per cent.).

2. Constant, static: in which the illness had run an unremitting course but had been static with no worsening or improvement for some time prior to admission—13 cases (15 per cent.).

3. Fluctuating: in which there had been periods of worsening and of relative improvement, but the patient at no time since the onset had been entirely free of symptoms—29 cases (33 per cent.).

4. Phasic: in which there had been a period, or periods, of remission of symptoms since their first onset—12 cases (13 per cent.).

The 13 per cent. of all patients showing a phasic course compares with only three of 37 patients (8 per cent.) in the obsessive-compulsive group. In four of the 12 phasic cases there was a definite affective element, all of them responding well to electroplexy.

Pollitt found that half of his patients showed an episodic course with an average of two previous attacks before the one bringing the patient under observation. While most writers stress fluctuations in course, usually coinciding with environmental stress, few others have found a truly phasic or episodic course common. Müller mentions the occurrence, and associated it with good prognosis; Rüdin states explicitly that less than 15 per cent. of his series ran a definitely phasic course, although of the 83 per cent. running a continuous course some had good and bad periods. The present finding that less than one in seven patients show a phasic course agrees with this exactly.

The discrepancy between the results may be verbal, for what one calls a good period of the illness another may consider to be normal if severe obsessional personality traits intervene between two attacks. It is more likely that the difference is real and due to different material. The greater number of Pollitt's non-leucotomized patients were out-patients seen in private practice and, indeed the outcome in those patients was rather better than in those in-patients leucotomized, strongly suggesting that cases differing widely in severity were contained in the series. His study indirectly supports Müller's observation that a phasic course is associated with a good prognosis.

No series is representative of the whole obsessional population and the truth probably lies between these results. The small number of severe classical obsessionals (three of 37) showing a phasic course and the fact that four of the total of 12 phasic cases responded to E.C.T. suggests that the more typical and severe the symptoms the less phasic the course and, as will be seen, the poorer the prognosis. It suggests too that affective features should be carefully searched for in phasic cases.

Prognosis

Method

An attempt was made to contact and assess all the patients but because of the wide geographical distribution of the sample only local cases were seen personally and replies to letters embodying an informal questionnaire were used in many cases. At least two attempts were made to reach each patient and letters were sent to the patient's next-of-kin and general practitioner who gave their own reports and were often able to help in tracing cases and persuading reluctant patients to write. In 64 (72 per cent.) of the 89 cases replies were received from both the patient and another informant, or personal examination was made. Of the remaining 25, one had died, 11 were untraced, and in 13 either the patient or another informant did not reply. Of the 78 patients traced adequate information was available for 64, or 82 per cent.

The minimum follow-up period was one year, the maximum 11. The mean follow-up period was 5·9 years, S.D. 3·47. Twenty-four cases were followed up for less than five years and 40 for more than five years.

The letters of enquiry asked for information about the patient's work record, social life, and course, symptoms and further treatment since leaving hospital. From the replies the following grading was made:

Grade A Symptom-free, able to lead a normal and full working and social life.

Grade B Symptoms much improved but not entirely free of them. Leading a full working life and making a reasonable social adjustment.

Grade C Symptoms unchanged or only minimally improved, but working in a job or at home, although with difficulty. Socially handicapped by illness.

Grade D Symptoms unchanged or worse, unable to hold employment or carry out household tasks. Socially isolated by illness or in hospital.

Grades A and B together form an "improved" category, Grades C and D an "unimproved" one. Similarly Grades A, B and C together comprise patients able to work or at least making some adjustment to their illness.

In considering the results the assumption is made that leucotomy was the only treatment given of lasting effect and these patients were considered separately from the remainder (18 cases). The mean follow-up for the leucotomized patients was 6·1 years. For these patients the period of follow-up dated from the date of operation; for the remainder from the date of discharge.

It is possible that the duration of follow-up may have an effect on outcome. To test this the results were compared for those patients assessed before and after a five-year period.

Under five years there were 12 improved and 12 unimproved; over five years there were 16 improved and 24 unimproved. Although the results after five years seem slightly worse the difference is not significant ($\chi^2=0·27$, P not significant) and it can be assumed that the follow-up was of sufficient length to give a true account of prognosis.

Results

TABLE X

Result of Follow-up: Non-leucotomized Cases

		Clinical Groups						
Results		Classical Nuclear	Phobic	Rumin-ative	Doubt-fully Schizo-phrenic	Affec-tive	Miscel-laneous	Total
Improved	(A)	0	1	0	1	2(1P)*	0	4
	(B)	1	5	1	3	2 P*	2	14
Unimproved	(C)	9	0	2	0	1 P*	0	12
	(D)	6	0	3	2	1	4	16
Total	..	16	6	6	6	6	6	46

* P=those patients whose illness had run a phasic course since discharge.

Of the patients not leucotomized (Table X) 18, (39 per cent.) are improved and 28 (61 per cent.) unimproved, yet 30 (66 per cent.) are able to hold some kind of employment and only 16 (34 per cent.) are totally handicapped by their

symptoms. All the phobic patients are improved and the worst results are found in the compulsive and ruminative groups where only two out of 22 patients show significant improvement. Three of the patients were in mental hospitals at the time of follow-up.

TABLE XI

Result of Follow-up: Leucotomized Cases

Results		Clinical Groups: Nuclear	Rumin-ative	Doubt-fully Schizo-phrenic	Affective	Miscel-laneous	Total
Improved	(A)	2	0	1	0	1	4
	(B)	5	1	0	0	0	6
Unimproved	(C)	3	0	0	0	0	3
	(D)	3	0	1	1	0	5
Total	..	13	1	2	1	1	18

Ten of the 18 leucotomized patients are improved (Table XI). Most of those so treated were classical compulsive cases. The operation used in all cases was standard prefrontal leucotomy, but undesirable personality change was infrequent. Many doctors and relatives mentioned slight changes in the improved cases but almost invariably made a comment to the effect that the good effects of the operation far outweighed any personality changes. In those unimproved the continuing symptoms were complained of and not side-effects of the operation, except in one patient who remains in hospital after a second leucotomy with persistent symptoms and marked deterioration in personality and habits. Two patients were still in hospital at the time of the follow-up.

The differences between those leucotomized and those not are more easily seen if they are compared as improved (A and B) and unimproved (C and D). Ten of the 18 leucotomized are improved (56 per cent.) and only 18 of the 46 who did not have the operation (39 per cent.) ($\chi^2=14{\cdot}5$, $P=<0{\cdot}01$). In the obsessive-compulsive cases the results are striking. Only one of the 16 not leucotomized was improved compared with seven of the 13 leucotomized.

These differences are in symptomatic improvement. If ability to work is used as a criterion of improvement the differences are less marked and do not reach statistical significance. Thirteen of the 18 leucotomized were working at follow-up (72 per cent.), compared with 30 of the 46 untreated (65 per cent.). In the nuclear group 10 of 13 leucotomized and 10 of 16 untreated are working.

The prognosis in obsessional illness has always been debatable. Farr and Stewart (6) in a lengthy follow-up of in-patient neurotics conclude that compulsive patients have a grave prognosis, partly because of the number of psychotic developments. The studies exclusively concerned with obsessional patients draw a more optimistic picture. Lewis examined 50 patients at least five years after treatment and found one-third symptom free, one-third improved and one-third unimproved. Rüdin found the outcome less satisfactory, with one-third running a long progressive course to end states of severe inhibition and inability to work, one-third unimproved and stationary and the remaining third notably improved, with 14 per cent. of the latter apparently cured. Despite these figures only 42 per cent. were unable to work at the time of follow-up.

Müller's follow-up extended over 25 years, the average age of the patients reaching 55 years at the end of that time. Sixteen of the 57 were symptom free and over half were improved. In a much shorter follow-up Pollitt found 70 per cent. symptom free or able to carry on a normal life, the figure dropping to 64 per cent. when the follow-up exceeded 4 years.

Judged by symptoms the present results are poor, especially in the classical cases, yet two-thirds were able to continue in employment. In course and prognosis the phobic states carry a uniformly good prognosis. As would be expected the depressive cases do well although relapses occur, but it is an unexpected finding that the doubtfully schizophrenic group did better than most although the numbers in this group are too small to be reliable.

The results as a whole are similar to Rüdin's who found one-third improvement and 5 per cent. apparent cure. The comparable figures here are 39 per cent. and 9 per cent. There is nothing in these findings comparable to the 70 per cent. found to be symptom free in Pollitt's shorter follow-up and the discrepancies suggest serious differences in sampling. The follow-up in the present series is not long enough to compare with Müller's finding of improvement in over half in later life.

Development of Schizophrenia

Four patients developed schizophrenia. All had been placed in the doubtfully schizophrenic group initially. Two of these cases showed an insidious progression to schizophrenia over many years. Their obsessional rituals became increasingly secretive and stereotyped and secondary symptoms of schizophrenia appeared. A third patient had a similar history and was leucotomized. Three years later he remained in hospital unimproved. The last patient was admitted in late adolescence with obsessional symptoms which developed into florid schizophrenia in four months. He did not respond to insulin coma therapy and prefrontal leucotomy was carried out six years ago. He is now teaching, having married and taken a university degree since operation; he is symptom free.

The incidence in the group is 6 per cent. In the two other mental hospital series the figures were 12 per cent. (Müller) and 10 per cent. (Rüdin), but in Pollitt's series, containing many out-patients, schizophrenia was found in less than 1 per cent.

Rosen (23), who investigated obsessional symptoms in a series of schizophrenic patients, found that the obsessional features persisted after schizophrenia was diagnosed and this was confirmed in all four cases. He found paranoid symptoms to be almost always present; here only one case showed paranoid features.

The outstanding feature here is the relatively low incidence of schizophrenia, considering the severity of the cases and the initial suspicion of schizophrenia in 15 cases. Some cases, doubtfully schizophrenic on admission, may well have shown definite schizophrenic symptoms quickly leading to classification under schizophrenia and exclusion from the present series as a result. Even if this occurred it was probably a rare happening, as Rosen found that only 3·5 per cent. of schizophrenic admissions showed obsessional symptoms.

Prognostic Indicators

Findings in the previous history were analysed to assess their relation to prognosis. Seven factors are shown in Table XII which deals with those cases

not leucotomized. Four reach acceptable levels of significance, the remaining three indicate trends. Other factors investigated which showed no significant relation to outcome were sex, marital status, positive family history, markedly

TABLE XII

Prognostic Indicators (Cases not Leucotomized)

		Improved (18)	Unimproved (28)	P Value
1. Diagnosis ..	Nuclear group ..	1	17	$\chi^2 = 13{\cdot}3$
	Other	15	13	$P = <0{\cdot}01$
2. Motor symptoms	Present	8	21	$\chi^2 = 5{\cdot}80$
	Absent	10	7	$P = <0{\cdot}02$
3. Childhood symptoms	Present	2	11	$\chi^2 = 5{\cdot}79$
	Absent	16	17	$P = <0{\cdot}02$
4. Onset-admission*	Under 5 years ..	11	10	$\chi^3 = 3{\cdot}96$
	Over 5 years ..	7	18	$P = <0{\cdot}05$
5. Anxiety and depression ..	Prominent	8	4	$\chi^2 = 3{\cdot}72$
	Minimal	10	24	$P = <0{\cdot}1$
6. Age of onset ..	Under 25	9	19	$\chi^2 = 2{\cdot}31$
	Over 25	9	9	$P = <0{\cdot}2$
7. Raven's matrices ..	Average and above	13	24	$\chi^2 = 2{\cdot}27$
	Below average ..	5	4	$P = <0{\cdot}2$

* The mean duration of symptoms in those improved was 3·7 years: in those unimproved 12·4 years.

obsessional pre-morbid personality, type of course, presence of precipitants and age on admission.

For the 18 leucotomized patients a similar analysis shows no significant differences; the number is too few to reveal trends at a statistically acceptable level. Nevertheless the results are of clinical interest.

TABLE XIII

Prognostic Indicators (Leucotomized Cases)

	Improved (10)	Unimproved (8)
Negative family history	8	4
Fluctuating or phasic course	6	3
Anxiety/depression prominent	4	1
Childhood symptoms absent	5	2
Precipitants	5	3
Above average intelligence	5	3
Previous personality not severely obsessional	8	6
Onset over 35	3	1

In Table XIII the items have been placed in rank order, those differing most being at the top of the list. The items provide a list of favourable prognostic indicators. The other factors investigated were the same as those considered for the cases not leucotomized: none showed any trend. In particular, there was

no difference in outcome of operation between those with and those without motor symptoms.

There is little information in previous work on the effect of different facets of the illness on outcome. Pollitt showed that the longer the duration the worse was the prognosis and the same holds in this series (Table XII).

More investigation has been carried out on the factors influencing the results with leucotomy. Partridge (18) on the basis of his follow-up of 24 patients thought that the decisive factor was "the entrenchment and standardization of the rituals". If symptoms were still variable improvement resulted; if not the prognosis was poor. Sargant and Slater (26) stress the good prognostic value of a well-adjusted pre-morbid personality, of late onset and of the presence of anxiety and tensions. Pippard (19) also stresses the importance of an "adequate" personality and late onset. He found no significant difference between patients with mainly "sensory" and patients with mainly "motor" symptoms but was impressed with the "intractability of long-ingrained habits of behaviour".

Their opinions are based on small numbers. It is worth comparing these impressions of leucotomized patients with the findings in those not leucotomized in this series. Many of the factors said to favour the outcome of operation are seen to be the same as those favouring spontaneous improvement. The prominence of affective symptoms, the absence of motor symptoms and late onset are all held to favour a good leucotomy result; here they are associated with spontaneous improvement. The nuclear group of obsessive-compulsive states corresponds closely to the cases with entrenched, standardized rituals which Partridge and Pippard considered to give poor operative results. In the 18 leucotomized cases in this series the difference in outcome between those with and without motor symptoms is negligible but comparisons with the obsessive-compulsive patients not subjected to operation shows a significant gain from the operation in these severe states with motor symptoms.

The results show that leucotomy is an effective treatment but cast doubt on the previously suggested indications for it. The present findings for those leucotomized indicate that the family history, the type of course and the presence of childhood symptoms are worth consideration and Sargant and Slater's attention to affective symptoms is supported.

Conclusions

In all large series of obsessional patients, including the present one, there is agreement on a number of findings. The incidence is always low and constant, the celibacy rate high, and social class and intelligence are above average. Childhood symptoms and precipitants are common and most show obsessional personality traits. A youthful onset and delay before admission are other repeated observations.

Most of these findings imply severity of the illness: its early commencement, its effect on marriage, the close ties with personality and the fact that social class and intelligence provide no protection against hospital admission. Severity was to be expected in the patients studied but when the variations in sampling between different series are taken into account the measure of agreement with previous series is surprising.

It has sometimes been suggested that there may be a qualitative difference between mild and severe obsessional states and even that there may be neurotic and psychotic varieties of obsessional illness. In the extreme represented by the patients in this series links with psychosis could be anticipated were these

suggested differences true. Schizophrenia was considered as a possible diagnosis in many but in fact the transition to schizophrenia seldom took place. It is possible to suggest other parallels with schizophrenia in the frequency of childbirth and adolescence as precipitants and the generally youthful onset. Yet it would be unwise to suggest that obsessional illness and schizophrenia are closely linked. As well as the association with schizophrenia, associations with depressive illness, anxiety and hysterical symptoms, and even with organic disease, are well known and have been found in these patients. There is nothing to suggest that associations with psychosis are more common than those with neurosis and there is no evidence from other findings to suggest any qualitative difference between these severe cases and the milder ones previously reported. All groups of obsessionals, whether they be out-patients or in-patients, show more similarities than differences.

The points of agreement with previous series of obsessional patients are in many cases points of difference from the control groups. The obsessional patients differ from both control groups more often than they resemble one or other of them. They are more intelligent and less fertile. Physical precipitants are commoner. They have more childhood symptoms, their illness starts earlier in life and the period between onset and admission is longer. They resemble the group of anxiety neurotics in two ways: high social class and a greater number of women; but they also resemble the hysterics in two ways; relative youth on admission and a high celibacy rate.

Symptomatically obsessional patients are obviously different from other neurotics. They also differ in these less direct measures. While the clinical psychiatrist would expect this, it is emphasized in view of the tendency among psychologists to align obsessional illness with anxiety neurosis under the dimension of dysthymia to the neglect of the special problems of obsessional personality and illness (5). Hamilton (9, 10), using a battery of performance tests, has been able to distinguish obsessional states from both hysteria and anxiety neurosis which is much more in keeping with both the direct and indirect clinical findings. Not only can the present group be distinguished from the other neurotics; in the few resemblances to their neurotic controls there is no tendency for the obsessionals to resemble the anxiety neurotics more than the hysterics.

The differences found are again indirect measures of severity, as were the similarities to previous obsessional groups. It follows that the severity of the obsessional cases in this group cannot be attributed entirely to selection by admission to hospital, for this factor applies equally to the control groups. The differences suggest the conclusion that obsessional states are more severe than other neurotic disorders.

The most controversial area investigated was the course and prognosis of the illness. A constant course was found in over half and a truly phasic course in less than one in seven. This agrees with other mental hospital findings but differes from Pollitt's observations on a sample containing more out-patients. Although the type of course was not significantly related to prognosis in this series, differences in outcome parallel the types of course found in different series. Pollitt's results after four years are much more encouraging than those of Lewis, Rüdin and those presented here and differ from them in finding a phasic course to be common.

The patients in this group would be expected to have a poor prognosis; all were in-patients, many could be called chronic on admission. Recovery is certainly rare, but improvement is found in over a third, and incapacity is

found in only a third. If such findings obtain in the most severe cases it can be assumed with confidence that the prognosis of obsessional illness in the total population is not at all poor.

Knowing the outcome in hospitalized obsessionals, the results of leucotomy in comparable cases can be re-appraised. The operation leads to symptomatic improvement, especially in typical cases with rituals, but makes little difference to working capacity. While the operation is clearly helpful, the existing indications for it are open to doubt as they have been shown to be indications that improvement is likely without recourse to surgery. Chronic cases with motor symptoms have always been considered poor prospects for leucotomy. It has been shown that, although the results may not compare with those obtained in less chronic cases with rituals absent or not established, the outcome is far better than in those not leucotomized.

In summary, this study which set out to examine the peculiarities of chronic severe obsessional states has shown that they differ little from other obsessional groups reported. The differences between the patients and the neurotic control groups are great and suggest that obsessional states are more serious conditions. Yet the outcome in the obsessional group is not disappointing; the method of selection ensures that the prognosis of obsessional illness can be no worse than the prognosis of these particular patients and among them symptomatic improvement was not rare and incapacity was the exception. Apart from spontaneous improvement it has been shown that treatment by leucotomy can give worthwhile results in patients previously thought unlikely to benefit from the operation.

Summary

The natural history of obsessional illness has been studied in 89 mental hospital in-patients. Diagnostically 37 were classified as obsessive-compulsive neurosis, 16 as phobic-ruminative, 14 were doubtfully schizophrenic, 10 showed depressive features and 12 were otherwise atypical.

The incidence was 0·9 per cent. of all admissions. The celibacy rate was 51 per cent., the fertility rate 1·1 per cent. Social class and intelligence were higher than in control groups of hysterics and anxiety states.

Childhood symptoms were seen in 36 per cent., precipitants of the illness were important in 69 per cent. Pregnancy was a common precipitant. The illness began early (mean 24·7 years) but admission was delayed (mean age 36·1 years). The majority (54 per cent.) showed a constant course; only 13 per cent. a definitely phasic one.

Sixty-four cases, 18 of whom were leucotomized, were followed up for an average of 5·9 years. Of those not leucotomized 39 per cent. were improved; and 66 per cent. were working. Of those leucotomized, 55 per cent. were improved and 72 per cent. working. In the typical obsessive-compulsive cases only one of the 16 not leucotomized was improved, compared with seven of the 13 leucotomized.

Spontaneous improvement was significantly associated with atypicality, absence of motor symptoms, absence of childhood symptoms, and a short duration prior to admission. It was concluded that chronicity and presence of motor symptoms were not contra-indications for leucotomy and that many of the current recommendations for leucotomy are indicators of spontaneous remission.

Spontaneous recovery in severe obsessional illness is rare, improvement common, and disablement only occurs in a minority.

Acknowledgments

I am indebted to Dr. P. K. McCowan and Dr. James Harper, past and present Physician-Superintendents of Crichton Royal, Dumfries, for permission to carry out this work and to Dr. A. C. Tait, Director of Clinical Research, for advice and criticism. Much of this paper formed part of a thesis for the degree of M.D. of the University of Edinburgh.

References

1. Berman, L., *J. nerv. ment. Dis.*, 1942, **95,** 26.
2. Blacker, C. P., and Gore, A. T., Triennial Statistical Report. 1949, 51, 1955. London: Bethlem Royal and Maudsley Hospital.
3. Eysenck, H. J., *Lancet*, 1943, 362.
4. *Idem, Dimensions of Personality*, 1947. London: Routledge and Kegan Paul.
5. *Idem, The Scientific Study of Personality*, 1952. London: Routledge and Kegan Paul.
6. Farr, C. B., and Stewart, G. M., *J. nerv. ment. Dis.*, 1942, **95,** 133.
7. Freeman, W., and Watts, J. W., *Psychosurgery*, 1950. 2nd edition. Oxford.
8. Greenacre, P., *Amer. J. Psychiat.*, 1923, **79,** 527.
9. Hamilton, V., *Brit. J. Psychol.*, 1957, **48,** 200.
10. *Idem, J. Ment. Sci.*, 1957, **103,** 666.
11. Himmelweit, H. T., *J. Personality*, 1945, **14,** 93
12. Janet, P., *Les Obsessions et la Psychasthénie*, 1908. Ed. 2. Paris.
13. Kallman, F. J., *Amer. J. Psychiat.*, 1946, **103,** 309.
14. Kraepelin, E., *Textbook of Psychiatry*, 1921. 8th German edition (trans. Barclay). Edinburgh: Livingstone.
15. Lewis, A. J., *Proc. Roy. Soc. Med.*, 1936, **29,** 325.
16. Mayer-Gross, W., Slater, E., and Roth, M., *Clinical Psychiatry*, 1954. 1st edition. Cassell.
17. Müller, C., *Nervenarzt*, 1953, **24,** 112.
18. Partridge, M., *Prefrontal Leucotomy*, 1950. Oxford.
19. Pippard, J., *J. Ment. Sci.*, 1955, **101,** 756.
20. *Idem, Proc. Roy. Soc. Med.*, 1956, **49,** 846.
21. Pollitt, J., *Brit. Med. J.*, 1957, *i*, 194.
22. Registrar General, *Statistical Review of England and Wales*, 1949. *Supplement on Mental Health*, 1953. London: H.M.S.O.
23. Rosen, I., *J. Ment. Sci.*, 1957, **103,** 773.
24. Ross, D., and Rice, D., *ibid.*, 1945, **91,** 495
25. Rüdin, E., *Arch. Psychiat. Nervenkrank.*, 1953, **191,** 14.
26. Sargant, W., and Slater, E., *Proc. Roy. Soc. Med.*, 1950, **43,** 1007.
27. Schneider, K., *Allg. Z. Psychiat.*, 1939, **112,** 17.
28. Slater, E., *J. Neurol. Neurosurg. Psychiat.*, 1943, **6,** 1.
29. Slater, P., *Brit. J. Psychol.*, 1945, **35,** 40.
30. Stengel, E., *J. Ment. Sci.*, 1945, **91,** 167.
31. *Idem, Proc. Roy. Soc. Med.*, 1956, **49,** 849.

PSYCHIATRIC HEADACHE

A CLINICAL STUDY

By

N. L. GITTLESON, M.A., B.M., B.Ch., D.P.M.

Registrar

Department of Psychiatry, Manchester Royal Infirmary

Introduction

Headache is a common problem (Rangell, 1953). Cohen (1939) concluded that relatively few cases were organically based and Shapiro (1955) in an American series found that only four out of a hundred cases presenting with headache could be explained on an organic basis, even though there are fifty odd causes of the symptom (Harris, 1936).

Headache with no obvious organic cause is a frequent symptom in psychiatric practice and is often an early one (Curran, 1939). Other authors have made the same point (Hazell, 1942; Grinker and Gottschalk, 1949; Brown, 1936). Lesse (1956), discussing atypical facial pain syndromes, stresses the frequency of an underlying involutional melancholia.

Shapiro (1955) divides the causes of headache into three groups. His first group is where the symptom is primarily determined by gross organic pathology, e.g. brain tumour. The second group is where a pathological physiological change can be demonstrated, e.g. fever, migraine, epilepsy. The third group is where no organic pathology or pathophysiology can be demonstrated. Shapiro goes on to state that although emotional factors can affect all three groups, in the third group it is the primary determinant of the headache.

This group consists of patients suffering from headache in association with personality disorders, a functional psychosis (schizophrenia or affective psychosis) or combination thereof. The headache of migraine, organic brain disease and epilepsy are excluded from this group as they fall into Shapiro's second group. In this study the term "psychiatric headache" is used to describe the headache of the third group. "Psychogenic headache" would be an unsuitable term to use in association with the functional psychoses. The term "tension headache" implies a greater understanding of causation than we in fact possess.

The previously cited authors all stress the obsessional nature of personality structures of patients with "psychiatric headache". This clinical impression was confirmed in a pilot study on an out-patient series.

If it could be shown that different patterns of headache are associated with different diagnostic categories, then this information would have diagnostic and predictive value.

This study was undertaken to examine the accuracy of these statements and to ascertain whether the headache was linked with other psychiatric variables.

Methodology

All patients admitted to the Manchester University Psychiatric Clinic over a two-year period, who complained of headache or head pains, either alone or

with other symptoms, were studied. Out-patients were excluded as it is not possible to investigate them as fully as in-patients. All patients had a routine physical examination and complete diagnostic and consultative facilities were available so that organic disease, including epilepsy, could be excluded. All patients were reviewed at a full Staff Conference.

Although Stenbäck (1954) points out many of the difficulties in the use of the migraine concept and denies its validity, it was felt that cases of migraine should be excluded from the series. The criteria used were those of most clinicians (Worster-Drought, 1939; Friedman, 1957; Cohen, 1939; Ebaugh and Drake, 1956; Friedman *et al.*, 1954). In no case was there any real doubt about the decision as to whether an individual did or did not have migraine. This group, termed the headache group, comprised 19 males (36 per cent.) with a mean age of 40·58 (range 23–60) and 34 females (64 per cent.) with a mean age of 43·03 (range 17–69).

The diagnostic categories were as follows: Schizophrenia: males 5, females 7; Schizo-affective Psychosis: males 0, females 1; Affective Psychosis: males 2, females 2; Affective Psychosis coupled with a marked personality disorder: males 6, females 7; Personality Disorder: males 6, females 17.

A parallel series of patients from a surgical ward of the hospital was studied, only those who denied that they suffered from headaches were included. Information was gathered about a family history of headache and a history of head injury. A thirty-minute interview specially directed towards assessing their personality was then given. Patients in this group who had taken medical advice on account of "nerve trouble" were excluded. This group, termed the surgical group, comprised 19 males with a mean age of 53·21 (range 33–83) and 34 females with a mean age of 42·68 (range 12–79).

A third group of patients comprised all those admitted to the Manchester University Psychiatric Clinic over the same period with the exclusion of cases with organic states and of course those suffering from non-organic headache. This third group included those diagnosed as migraine. The third group of patients were all seen at a full Staff Conference (where they were interviewed) and all except eight were seen personally, with a view to personality assessment.

This third group, termed the non-headache group, comprised 69 males (37·1 per cent.) with a mean age of 39·16 (range 16–73) and 117 females (62·9 per cent.) with a mean age of 41·09 (range 18–75). The diagnostic categories were as follows: Schizophrenia: males 15, females 23; Schizo-affective Psychosis: males 2, females 2; Affective Psychosis: males 14, females 44; Affective Psychosis coupled with a marked personality disorder: males 10, females 5; Personality Disorder: males 28, females 43.

Results and Discussion

Diagnostic Categories

Comparing the incidence of diagnostic categories in the headache and non-headache groups (combining the sexes) we obtain no significant difference for schizophrenia. There is a significantly lower incidence of patients classified as suffering from uncomplicated affective psychosis in the headache group (chi-squared=13; 0·01>P). There is a significantly greater incidence of patients in the headache group classified as suffering from affective psychosis coupled with a marked personality disorder (chi-squared=9; 0·01>P). Combining uncomplicated affective psychosis and affective psychosis coupled with a marked personality disorder there is no significant difference. This suggests that affective

psychosis *per se* considered independently of whether or not there is an associated personality disorder is evenly distributed between the headache and non-headache groups.

Whether the sexes are considered separately or together, there are no significant differences between the incidences of uncomplicated personality disorder in the two groups. However, combining personality disorders with affective psychosis coupled with a marked personality disorder, we find that there is a significantly higher incidence in the headache group taking both sexes together (chi-squared=6·9; 0·01>P). This suggests that personality disorder *per se* considered independently of whether or not there is an associated affective psychosis is more frequent in the headache group. Further analysis shows that this higher incidence is present only in the women. (For women only, chi-squared=8·08; 0·01>P. For men only, chi-squared=0·13; 0·8>P>0·7).

Mean Ages of Diagnostic Categories

There are no significant differences between the mean ages of the diagnostic groups of patients suffering with headache and the mean ages of the corresponding diagnostic groups of those patients not suffering with headache.

Sex Ratio

In the headache group 64 per cent. were women. Friedman (1957) and Friedman *et al.* (1954) found that of sufferers from tension headache 65 per cent. were women. In two series of atypical face pains, Campbell and Lloyd (1954) found a figure of 60 per cent., McElin and Horton (1947) found women twice as numerous as men. It could be argued, however, that atypical face pain is not the same symptom-complex as headache and head pains. H. Wilson (1938) found only a slight preponderance of women in patients referred for psychotherapy. The non-headache group of patients shows a similar preponderance of women and the difference of sex ratios is not significant (chi-squared=·11; 0·8>P>0·7).

Age of Onset

The ages of onset alongside the age ranges of the patients are shown in Table I.

TABLE I

Years	Age of Patient with Headache		Age of Onset of Headache	
	Men	Women	Men	Women
0–10	0	0	1	2
10–19	1	2	1	2
20–29	4	3	5	4
30–39	4	12	3	13
40–49	3	5	5	5
50–59	6	4	4	5
60–69	1	8	0	3

It can be seen that the scatter is wide, but it agrees approximately with Friedman *et al.* (1954), who found that 55 per cent. had an onset between 20 and 40 years of age. McElin and Horton (1947) studying atypical face pain found a maximum onset between 30 and 50 years.

Duration of the Headache Symptom

The total duration of headache as a symptom is shown in Table II.

TABLE II

Duration of Headache in Years	Men	Women
0– 1	6	9
1– 2	4	8
2– 5	4	9
5–10	3	2
10–20	2	3
20–40	0	2
40–50	0	1

This scatter in view of the heterogenicity of the diagnostic groups is not surprising. Those with symptoms of very long duration (over five years), were suffering from personality disorders.

Family History of Headache and History of Head Injury

The family histories of the headache group were compared with the control group of surgical patients. They were also compared for a history of head injury. The family history was positive for headache in 4 men and 11 women in the headache group, and in 3 men and 10 women in the surgical group.

Friedman (1957) and Friedman *et al.* (1954) found a positive family history in tension headache in 40 per cent., Stenbäck (1954) found a family history of headache in 61 per cent. This series gives 21 per cent. for men and 32 per cent. for women with no significant difference between the headache group and surgical patient controls.

A history of head injury associated with loss of consciousness was elicited in 2 men and 2 women in the headache group and in 1 man and 6 women in the surgical group. A history of head injury not associated with loss of consciousness was elicited in 7 men and 10 women in the headache group and in 8 women and 9 men in the surgical group.

There is thus no significant difference between the groups for history of head injury which is 47·4 per cent. for men and 35·3 per cent. for women. Stenbäck (1954) found an incidence of 17·2 per cent. H. Wilson (1938) found a history of injury in only four out of seventy-five, i.e. 5·3 per cent. The higher incidence in this series is probably due to the fact that all trauma remembered was counted as an injury. The criterion therefore was not its severity, but whether it was remembered.

Variation of Effect of Menses

Wilson (1938) was unable to discover any relationship between the sexual life and the headache pattern. No attempt was made in this study to assess the degree of sexual adjustment. Enquiry was made, however, about the effect of the menses in the female patients, and all of them stated that the menses, especially the premenstrual and first days, worsened the headache if it was present at that time.

Constancy of the Headache

Sixteen of the male patients (84·2 per cent.) and 25 of the female patients (73·5 per cent.) suffered from the headache constantly or every day. One male

patient (5·3 per cent.) and 3 female patients (8·8 per cent.) suffered more than three attacks per week. Two male patients (10·5 per cent.) and 6 female patients (17·7 per cent.) suffered less than three attacks per week.

Friedman (1957) found those with daily headache formed 30 per cent. and were the largest group, and in an earlier paper (Friedman *et al.*, 1954) he found that 50 per cent. had headache daily or constantly. Hazell (1942) and Ebaugh and Drake (1956) stress the constancy of the headache. A similar viewpoint is stressed in regard to atypical face pain by Frazier and Russell (1924) and McElin and Horton (1947). Curran (1939) stresses the unpleasant quality of the headache in agreement with Butler and Thomas (1947). Hazell (1942), Friedman *et al.* (1954), Friedman (1957) and Shapiro (1955) stress the vagueness and variability of the headache when the patient is "pinned down" to describe. This was not so in this series, but this may have been due to the relatively high proportion of obsessional personalities in the group.

Description of Headache

Wilson (1938) pointed out that nearly half the terms used were not considered exaggerated. In this series seven men (37 per cent.) and fourteen women (41 per cent.) were considered to be exaggerating, in most cases, however, it was not gross. This opinion was based on observing the patients during occupational therapy, etc., and is extremely subjective, Amongst women, the phrase "like my head pressed between two boards", was once used by a hysteric. "As though a hammer is hammering on my head" was used once by an obsessional. "As though something pushed in" by an obsessional. One obsessional used the phrase "it's a crawling feeling". One hysterical man used the phrase "crawling wetness". Even so, odd turns of phrase by no means suggest schizophrenia or hysteria. Nine male patients (47 per cent.) and twenty female patients (59 per cent.) described the sensation as severe.

The terms used to describe the sensation were as follows (each word used by the patient to express a component of the sensation was noted). Pressure: 14 men (74 per cent.) and 24 women (71 per cent.); Aching: 5 men (26 per cent.) and 16 women (44 per cent.); Pain: 4 men (21 per cent.) and 11 women (32 per cent.); Burning: 3 men (16 per cent.) and 7 women (21 per cent.); Tight: 3 men (16 per cent.) and 6 women (18 per cent.); Throbbing: 2 men (11 per cent.) and 6 women (18 per cent.); Numb: 2 men (11 per cent.) and 1 woman (3 per cent.); Sharp: 1 man (5 per cent.) and 6 women (18 per cent.); Boring: 2 men (11 per cent.) and 3 women (9 per cent.); "Like a band round the head": 2 men (11 per cent.) and none of the women; Stabbing: 4 women (12 per cent.); Bursting: 4 women (12 per cent.). No men used the last two descriptions.

It can be seen that pressure and aching are the most commonly used terms. This is in agreement with the majority of clinical opinions such as those of Curran (1939), Wilson (1938), Chideckel (1939), Hazell (1942), Friedman *et al.* (1954), Harris (1936) and Shapiro (1955). Worster-Drought (1939) states that the headache associated with mild psychotic depression is a feeling of "oppression".

The views of Butler and Thomas (1947) that the sensation is a strange and terrifying feeling, and of Ebaugh and Drake (1956) that it is boring or like a tight hand are not supported by this series. Throbbing sensations do not appear very often. Harris (1936) states that local tenderness is common. Hazell (1942) denies this. Local tenderness was present in this series in two men (11 per cent.) and five women (15 per cent.).

Site of Headache

The sites of the headache were as follows: Occipital: 6 men (32 per cent.) and 16 women (47 per cent.); Frontal: 14 men (74 per cent.) and 29 women (85 per cent.); Temporal: 8 men (42 per cent.) and 13 women (38 per cent.); Vertical: 9 men (47 per cent.) and 16 women (47 per cent.); Facial: 3 men (16 per cent.) and 9 women (26 per cent.); Eyelids and Eyes: 5 men (26 per cent.) and 13 women (38 per cent.).

These results are in agreement with the views of Grinker and Gottschalk (1949) and Wilson (1938). Friedman (1957) and Ebaugh and Drake (1956) describe tension headache as occipito-frontal. Harris's view that the commonest site is the vertex is not supported (Harris, 1936), nor is the view of Worster-Drought that the headache is occipito-vertical.

Friedman *et al.* (1954) found only 10 per cent. were unilateral. In this series one man (5 per cent.) and seven women (21 per cent.) had unilateral symptoms. Unilaterality showed no relationship to site. The male patient was a hysterical personality with endogenous depression. The women comprised two hysterical personality disorders, three obsessional personality disorders, one schizophrenic with an obsessional personality and one obsessional with depressive psychosis. Unilaterality did not appear to have any diagnostic or other significance.

Associated Circumstances

Twelve men (63 per cent.) and seventeen women (50 per cent.) said the headache limited their activity. In fifteen (79 per cent.) of the men and twenty-eight (82 per cent.) of the women a precipitating cause was found. These causes came under three headings. First the onset of a psychosis—where it was in fact an early symptom and often the sole one for weeks or months. Second, external environmental traumatic events. Third, the development of symptoms of a personality disorder either with or without any apparent external trigger. Six men (32 per cent.) showed diurnal variation—the headache being in all six cases worse in the morning and all were suffering from depressive psychoses. The other thirteen showed no diurnal variation. Seven women (21 per cent.) showed diurnal variation worse in the morning. These comprised four patients suffering from depressive psychosis, one from paraphrenia and one from schizo-affective psychosis. Four women (12 per cent.) were worse in the evening, two with depressive psychosis (one of whom felt worse in the evening) and two obsessionals.

Response to Drugs

The response to drugs was as follows: Ten men (53 per cent.) and eighteen women (53 per cent.) stated that the headache responded to sedatives. Seven men (37 per cent.) and seven women (21 per cent.) stated that the headache responded to analgesics. Two men (10 per cent.) and nine women (26 per cent.) found the headache did not respond to either type of drug.

In no case was there difficulty in deciding that the sensation did not follow an anatomical distribution.

Causation of the Headache

All patients were asked what they thought was the cause of their headache. The replies of "nerves". "worry", "anger", "I get tensed up" and "when I get overstrained or overexcited", are collected together below under the heading

"nerves", which was the commonest word used. Twelve men (63 per cent.) and twenty women (59 per cent.) gave the cause as "nerves". Six men (32 per cent.) and thirteen women (38 per cent.) gave other causes, and one man (5 per cent.) and one woman (3 per cent.) did not know what the cause might be. It was surprising that so many patients had one sort of insight at least, into their condition.

Various views have been put forward to explain the mechanism by which the headache is produced. Friedman *et al.* (1954) believe that somatic muscle contraction or autonomic nervous system changes causing blood vessel changes are implicated and Fenichel (1946) agrees. Stenbäck (1954), though rejecting the concept of migraine, separates out these two types of headache. McElin and Horton (1947), talking of atypical facial pain, agree. Chideckel (1939) suggests that emotion may release some kind of toxin that alters the secretion of cerebrospinal fluid by the choroid plexus. Kubie (1953) suggests that tensions and emotions generated psychologically are converted into autonomic changes via the visceral brain—the rhinencephalon. Some clinicians, Grinker and Gottschalk (1949) and Rosenbaum (1947) stress anger, hate or frustration which cannot be expressed as a determinant of the headache. While Rosenbaum (1947) states that their feelings may be conscious or unconscious, others (Brenner *et al.*, 1949; Shapiro, 1955; Eisenbud, 1937), stress the unconscious nature of the hostility, aggression or conflict. Eisenbud implanted complexes hypnotically into a hysteric suffering from headache; post-hypnotically he could reproduce the headache by touching on the implanted complex.

The importance of the head to the patient has been discussed elsewhere in another study. Wolff (1948) stresses the fact that misinterpretation of normal head sensations is due to previous conditioning experiences. These experiences may well act by altering the "Gestalt" of the head in the body image.

Relationship to Personality

Shapiro (1955), Engel (1956, 1951), Grinker and Gottschalk (1949), Rosenbaum (1947), Wilson (1932) and Sperling (1952) all stress that the majority of patients had obsessional personalities with a relatively small number of hysterical personalities. Lesse (1956), discussing psychogenic atypical facial pain syndromes, agrees.

The various obsessional and "masochistic" traits which are so frequently mentioned in the literature fit well into the group of "insecure personalities" described by Schneider (1958), which includes the "sensitives" of Kretschmer (1952) and the obsessional. The attention-seeking personality group of Schneider (1958) corresponds to the hysterical personality described by Mayer-Gross *et al.* (1954).

The headache group, the surgical patient group and the non-headache group admitted over the same period (excluding organic syndromes), were compared clinically for assessment of personality. The headache group and the surgical group were all seen personally—the former in addition to a full review including the life history at a full Staff Conference. The non-headache group were all reviewed at a full Staff Conference and all but eight were seen personally in addition.

In assigning the ratings, the term "attention-seeking—personality disorder (hysterical)" was used only if there was definite evidence of frank conversion symptoms. The term "insecure traits" was used to label all those patients who showed marked lifelong sensitive or obsessive compulsive traits. Checking and

morbid doubt were specially investigated. Feelings of insecurity, tidyness, meticulousness, etc., were not sufficient in themselves to place a patient in this group unless severe. The term "insecure personality disorder" was used only if frank obsessive compulsive symptoms were present and if in addition the patient felt that they had "got out of hand" or he wished he could "stop it". The term "personality disorder" was used in Schneider's sense (1958), namely "abnormal personalities who either suffer personally because of their own abnormality or make the community suffer because of it". Phobias, unless gross and crippling, were not deemed sufficient as they are widely spread across the population.

The results are shown in Table III. The pre-morbid personality was assessed and classified independently of whether or not it was associated with a psychosis, that is, independently of the diagnostic category.

TABLE III

Pre-morbid Personality

Schneider's term ..	Attention-seeking Personality Disorder	Insecure Traits	Insecure Personality Disorder	Others
Common term ..	Hysterical Personality Disorder	Obsessional Traits	Obsessional Personality Disorder	Others
Men:				
Headache group ..	2 (11%)	3 (16%)	9 (47%)	5 (26%)
Non-headache group (Group III)	2 (3%)	15 (22%)	16 (23%)	36 (52%)
Surgical group ..	0	3 (16%)	2 (11%)	14 (74%)
Women:				
Headache group ..	4 (12%)	6 (18%)	24 (71%)	0
Non-headache group (Group III)	21 (18%)	19 (16%)	12 (10%)	65 (56%)
Surgical group ..	0	4 (12%)	3 (9%)	27 (80%)

Approximate percentages only.

Personality assessment is extremely subjective and difficult to quantify. The unreliability of the basic data and therefore of any further analysis based on them must be stressed.

By combining patients classified as possessing insecure traits and those classified as suffering from insecure personality disorders one can compare the incidence of "insecurity" as opposed to "non-insecurity" ("Attention-seeking personality disorders" and "Others") in the headache and non-headache groups.

The male patients show no significant difference in the incidence of "insecurity" between the headache group (63 per cent.) and the non-headache groups (45 per cent.) (chi-squared$=1\cdot32$; $0\cdot3>P>0\cdot2$). The female patients show a greater incidence of "insecurity" in the headache group (89 per cent.) than in the non-headache group (26 per cent.). The difference is statistically highly significant (chi-squared$=39\cdot2$; $0\cdot01>P$).

For the male patients the incidence of those classified as suffering from an insecure personality disorder was not significantly different in the headache group (47 per cent.) as compared with the non-headache group (23 per cent.) (chi-squared$=3\cdot17$; $0\cdot10>P>0\cdot05$).

The female patients showed a greater incidence in the headache group of those classified as suffering from an insecure personality disorder (71 per cent.) than in the non-headache group (10 per cent.), and this difference is highly significant statistically (chi-squared=49·5; 0·01>P).

Patients possessing insecure traits seem to be distributed more or less evenly throughout the headache, non-headache and surgical groups.

The preponderance of "insecurity" in the female patients with headache might therefore be due to a preponderance of sufferers from a frank insecure personality disorder rather than to a preponderance of patients possessing insecure traits only. In order to test this hypothesis, the relative incidence of possessors of insecure traits versus the incidence of those suffering from a frank insecure personality disorder was compared in the headache and non-headache groups.

Of the twelve male patients in the headache group possessing "insecurity", nine (75 per cent.) had frank insecure personality disorders. Of the thirty-one male patients in the non-headache group possessing "insecurity", sixteen (52 per cent.) had frank insecure personality disorders. This difference is not statistically significant (chi-squared=1·10; 0·3>P>0·2). This is in agreement with the previous finding that the male patients of the headache group do not show a preponderance of "insecurity" compared to the non-headache group. Of the thirty female patients in the headache group possessing "insecurity" twenty-four (80 per cent.) had frank insecure personality disorders. Of the thirty-one female patients in the non-headache group possessing "insecurity" twelve (39 per cent.) had frank insecure personality disorders. This preponderance of sufferers from frank insecure personality disorder in the headache group possessing "insecurity" is statistically highly significant (chi-squared= 9·11; 0·01>P). There is no significant difference in incidence of those patients possessing insecure traits only, between the female patients in the headache group (18 per cent.) and those in the non-headache group (16 per cent.) (chi-squared=0·046; 0·9>P>0·8). One may conclude therefore with a high degree of statistical probability that the preponderance of "insecurity" in the females of the headache group is due to the predominance of sufferers from a frank insecure personality disorder. It follows therefore that insecure traits themselves are not strongly associated with sufferings from psychiatric headache.

If the insecure traits are developed to the extent of causing society or the patient to suffer because of these traits then this constitutes a personality disorder in Schneider's (1958) sense. The female patients suffering with "psychiatric" headache show a marked preponderance of patients with such an insecure personality disorder as compared to the non-headache control group.

Comparison of the mean age of each personality group in those patients with headache with the mean age of the corresponding personality group in those psychiatric patients without headache showed no significant differences.

There were no significant differences between the distribution of the following factors amongst the various personality groups of those patients suffering from headache.

Age of onset of headache, age of the patient, duration of symptoms, constancy of duration of the headache, "exaggeration" of symptoms, severity of headache, terms used to describe the headache, site of headache, unilaterality or bilaterality, limitation of activity by the headache, diurnality or its absence, response or lack of response to sedatives or analgesics or both, or response to treatment.

The replies given by patients to the question asking them for their views as to the cause of the headache can be classified as "nerves" and "non-nerves". The latter is made up of "other causes" and "don't knows".

If those classified as "insecure personality disorder" are compared with the group named here as "other personalities" formed of "attention-seeking personality disorder", "insecure traits" and "others", we obtain the following:

Of the nine male patients suffering from an insecure personality disorder (whether or not in association with a psychosis) eight (89 per cent.) gave the cause as "nerves". Of the ten male patients in the group named here as "other personalities" four (40 per cent.) gave the cause as "nerves". The number of male patients is just too small to be significant but is similar in pattern to the replies of the female patients. Of twenty-four female patients rated as suffering from an insecure personality disorder (whether or not in association with a psychosis) eighteen (75 per cent.) gave the cause as "nerves". Of the ten female patients in the group named here as "other personalities" two (20 per cent.) gave the cause of the headache as "nerves". This difference is significant statistically (chi-squared$=6{\cdot}69$; $0{\cdot}01>P$).

If the male and female patients of the headache group are combined the result is as follows: of thirty-three patients suffering from an insecure personality disorder (whether or not in association with a psychosis) twenty-six (79 per cent.) gave the cause as "nerves". Of the twenty patients in the group named here as "other personalities" six (30 per cent.) gave the cause as "nerves". This difference is even more significant statistically (chi-squared$=10{\cdot}43$; $0{\cdot}01>P$).

It can be concluded therefore that those patients who recognize the "psychiatric" nature of their headache are much more likely to be classifiable as suffering from an insecure personality disorder (whether or not they are also suffering from a psychosis in addition) than those who do not possess this insight.

A surprising finding was five cases (9 per cent.) in the surgical control group, who had gross and partly disabling obsessive compulsive symptoms which would have been quite severe enough to bring them within the range of a psychiatric clinic. None of these patients had in fact ever taken medical advice about their obsessive-compulsive symptoms.

Pattern of Headache

No significant differences between the patterns of headache could be discerned in the various diagnostic categories. The headache was, so to speak, the same syndrome whatever the associated diagnostic category.

There were also no significant differences in the headache patterns when considered in relation to the various personality groupings except for the patients' view of the "cause" which has previously been discussed.

The descriptions of the headache given by patients rated as suffering from attention-seeking personality disorders tended to be more often rated as "exaggerated". The ratings were as follows: patients suffering from an attention-seeking personality disorder: two men, of whom one exaggerated; four women of whom three exaggerated. Patients possessing insecure traits: three men of whom two exaggerated; six women of whom two exaggerated. Patients suffering from an insecure personality disorder: nine men, of whom three exaggerated; twenty-four women of whom nine exaggerated. Of five men possessing other personality-structures, one exaggerated. There are no significant differences between the incidence of "exaggeration" in any one personality group as opposed to the other personality groups combined.

It must be stressed, however, that this assessment is an extremely difficult one to make and one would be most reluctant to place much value on it. Indeed, one was impressed by the similarity of the complaints of patients with widely differing psychiatric conditions and personality assessments.

Those patients with organic brain disease such as dementia, toxic confusional states, Korsakow's psychosis—which are not included in this series—showed more similarities to the psychogenic headache group than differences.

One female schizophrenic patient gave a classical description of "psychiatric headache". Asked for her views as to its cause, she replied: "It's done to me by that policeman with a machine." Wilson (1938) was unable to discern any syndromes with any particular distribution or type of pain though his series excluded psychotics and frank neurotics. He states that "psychogenic cephalgia" is a good example of the way in which psychoneurotic symptoms may crop up in any form of neurosis.

Curran (1939) believes that headache is a symptom that can be encountered in every type of mental disorder. Hazell (1942) stresses that "psychogenic headache is but one symptom of a neurosis or psychosis". Grinker and Gottschalk (1949) and Brown (1936) agree that headache is often the early symptom of a psychosis and this series confirms their view. Mayer-Gross (1938) and Eugen Bleuler (1911) state that headache is often an early symptom of schizophrenia and that it is often not described in a bizarre way, but more often as what would now be called a typical "tension headache". Eugen Bleuler (1916) considered that anxiety is the symptom most frequently accompanied by physical symptoms, such as headache, which he considers as one form of "localization" of the anxiety. Schneider (1959) points out that melancholia is often sharply localized as a body feeling ("vital feeling") in the forehead, chest and stomach as a sense of apprehension or weight, or, as Worster-Drought (1939) puts it, an "oppression".

As anxiety is an almost universal symptom in psychiatric disorder, this would explain in part the occurrence of headache in all forms of mental disorder. This series suggests that psychogenic headache occurring in diverse types of psychiatric disorder tends always to be the same syndrome. It is tempting to postulate tentatively that psychogenic headache is perhaps a preformed mechanism, which can be triggered by various types of illness or stress. The predominance of patients suffering from insecure (obsessional or anankastic) personality disorder in the females of the headache group is striking. It might be tentatively suggested that the premorbid personality structure is a more important determinant than the psychiatric diagnostic category.

Relationship to Depersonalization

In view of the frequency of depersonalization in patients with self insecure personalities, it was felt worthwhile to investigate it in this series.

Curran (1939) points out that patients in a depersonalized state often complain of their heads and that this is because the head is felt to be the seat of the Ego. The last statement has been investigated in another study.

The headache group was investigated by personal interview for the presence or absence of depersonalization and the results are as follows: three out of a total of nineteen male patients were depersonalized, i.e. 16 per cent. approximately. Fifteen out of a total of thirty-four female patients were depersonalized, i.e. 44 per cent. approximately. Thus more than half were not depersonalized (84 per cent. of the males and 56 per cent. of the females).

There did not appear to be any correlation between depersonalization and exaggeration. Of the seven male patients who were assessed as exaggerating, none was depersonalized. Of the fourteen women patients who were assessed as exaggerating six were depersonalized and eight were not.

Response to Treatment

Treatment was always directed towards the total psychiatric picture. The headache itself was treated with aspirin or codeine and if necessary additional barbiturate sedation. All forms of physical treatment including electro-convulsive therapy and modified insulin were used. Tranquillizing, anti-depressant and sedative drugs were also used. All patients received psycho-therapy and routine occupational therapy. Psychotherapy was never directed specifically against the headache but towards the total psychiatric picture.

Response to treatment was considered successful only if the patient said that the headaches had "completely gone" or were "no trouble at all now". Anything less was taken as failure. This assessment, of course, applied only to the headache and not the overall psychiatric condition. Eight out of a total of nineteen (42 per cent.) male patients were rated as having responded and twenty out of a total of thirty-four (59 per cent.) female patients were rated as having responded. These results do not show a sex difference significant at the one in ten level.

The response to treatment of the headache followed the course of the underlying psychiatric condition in every case. It ran parallel with the depressive psychosis. Patients suffering from schizophrenia or schizo-affective psychosis showed an improvement in the headache which paralleled the change in the psychopathology. It did not appear to follow the so-called social improvement. It was noticeable that at a certain level of improvement the headaches dis-appeared in the course of a day or two thus suggesting that some kind of threshold was involved. Relapse or recurrence of any psychosis was always accompanied by a return of the headache.

Patients suffering from personality disorders had usually been admitted following some crisis which had produced disabling symptoms. If the crisis could be dealt with then the headache paralleled the other symptoms and again disappeared in a day or two, again suggesting that one was dealing with a threshold phenomenon.

The ultimate prognosis in all cases depended on whether the underlying psychosis or environmental crisis was amenable to treatment.

Conclusions

In this series the apparent preponderance of female patients is but a fair sample of the total admissions. It is not suggested that a psychiatric clinic necessarily admits a random sample of the population from the viewpoint of the sex ratio.

There is no evidence that previous trauma to the head is a determinant of "psychiatric headache". The family history does not appear to be significant, nor the presence or absence of depersonalization.

The female patients suffering from headache show a preponderance of patients assessed as suffering from an insecure personality disorder, either alone or in combination with a psychosis. Such patients are likely to attribute the headache to "nerves" and this finding may have some dubious diagnostic value.

It is concluded that "psychiatric headache" by which is meant that headache associated with personality disorders or a functional psychosis or combinations thereof, tends always to be the same syndrome irrespective of diagnostic category or personality structure.

The syndrome is a bilateral, constant, frontal pressure. It is often the first symptom of a psychiatric illness. So-called "bizarre" terms are rarely used in its description. The prognosis of the headache depends on that of the associated or underlying psychiatric disorder.

It is tentatively suggested that "psychiatric headache" is a pre-formed mechanism triggered by various stresses, which is more likely to be possessed by patients suffering from insecure personality disorders than patients with other personality structures, irrespective of whether there is or is not an associated psychosis.

Summary

All patients suffering from psychogenic headache, alone or with other symptoms, who were admitted as in-patients over a two-year period to the Psychiatric Unit of the University of Manchester were studied. Patients with migraine or organic brain disease were excluded.

The group comprised nineteen male and thirty-four female patients. The patients suffering from headache were compared with all the other patients, 69 males and 117 females, admitted to the Unit over the same period with the exclusion of patients with organic brain disease. Amongst the female patients the headache group contained a significantly higher proportion of patients classified as suffering, alone or in combination with a psychosis, from an insecure personality disorder (which corresponds to the anankastic or sensitive obsessional personality disorder.)

Within the headache group the pattern of headache was strikingly constant amongst the various diagnostic and personality groups. The pattern was that of a constant bilateral frontal pressure. It is tentatively postulated that "psychiatric headache" is perhaps a pre-formed mechanism which can be triggered by many stresses.

This study suggests that female sufferers from an insecure personality disorder are more likely to possess this mechanism than those possessing other personality structures. They are also more likely to consider the headache as being caused by "nerves".

It was found that the prognosis of the headache was that of the underlying psychiatric condition.

Acknowledgments

I am indebted to Professor A. M. Boyd of Manchester University for permission to interview patients under his care. My thanks are also due to Professor E. W. Anderson for helpful encouragement and permission to publish; and to Dr. J. Hoenig for stimulating criticism and advice throughout the study.

References

Bleuler, E., *Textbook of Psychiatry*, 1916, (transl. 1951 by Brill, A. A.). U.S.A.: Dover Publication Inc., p. 121.

Idem, *Dementia Praecox*, 1911, (transl. 1950 by Zinkin, J.). New York: International Universities Press, p. 253.

Brenner, C., Friedman, A. P., and Carter, S., *Psychosomatic Med.*, 1949, **11**, 53.

Brown, F., *J. Ment. Sci.*, 1936, **82**, 295.

Butler, S., and Thomas, W. A., *J. Amer. Med. Ass.*, 1947, **135**, 967.

Campbell, A. M. G., and Lloyd, J., *Lancet*, 1954, *ii*, 1034.

CHIDECKEL, M., *Medical Record*, 1939, **149,** 339.
COHEN, H., *Brit. Med. J.*, 1939, *ii*, 713.
CURRAN, D., *ibid.*, 1939, *ii*, 717.
EBAUGH, F. G., and DRAKE, F. R., *Amer. J. Med. Sci.*, 1956, **232,** 105.
EISENBUD, J., *Psychiatric Quarterly*, 1937, **11,** 592.
ENGEL, G. L., *Psychosomatic Med.*, 1951, **13,** 375.
Idem, ibid., 1956, **18,** 334.
FENICHEL, O., *The Psychoanalytic Theory of Neurosis*, 1946. London: Routledge & Kegan Paul, p. 253.
FRAZIER, C. H., and RUSSELL, E. C., *Arch. Neurol. and Psychiat.*, 1924, **11,** 557.
FRIEDMAN, A. P., VON STORCH, T. J. C., and MERRITT, H. H., *Neurology*, 1954, **4,** 773.
Idem, Calif. Med., 1957, **87,** 15.
GRINKER, R., and GOTTSCHALK, L., *Psychosomatic Med.*, 1949, **11,** 45.
HARRIS, W., *Practitioner*, 1936, **136,** 289.
HAZELL, K., *Medical Press*, 1942, **208,** 219.
KRETSCHMER, E., *A Textbook of Medical Psychology* (transl. by Strauss, E. B.), 1952. London: The Hogarth Press, p. 263.
KUBIE, L. S., *Psychosomatic Med.*, 1953, **15,** 1.
LESSE, S., *J. Nerv. and Ment. Dis.*, 1956, **124,** 346.
MAYER-GROSS, W., *Brit. Med. J.*, 1938, *ii*, 936.
Idem, SLATER, E., and ROTH, M., *Clinical Psychiatry*, 1954. London: Cassell & Co., 123.
MCELIN, T. W., and HORTON, B. T., *Ann. Int. Med.*, 1947, **27,** 749.
RANGELL, L., *Psychosomatic Med.*, 1953, **15,** 22.
ROSENBAUM, M., *Dis. Nerv. System.*, 1947, **8,** 252.
SCHNEIDER, K., *Psychopathic Personalities* (transl. by M. W. Hamilton), 1958. London: Cassell, p. 85.
Idem, Clinical Psychopathology (transl. by M. W. Hamilton), 1959. New York and London: Grune & Stratton, pp. 136, 149.
SHAPIRO, M. F., *New York State J. Med.*, 1955, **55,** 2347.
SPERLING, M., *Psychoanalytic Review*, 1952, **39,** 152.
STENBÄCK, A., *Acta Psychiat. Neurol. Scand.*, 1954, Suppl. 92.
WILSON, D. C., *J. Amer. Med. Ass.*, 1932, **99,** 813.
WILSON, H., *Lancet*, 1938, *i*, 367.
WOLFE, H. G., *Headache and Other Head Pains*, 1948. New York: Oxford University Press.
WORSTER-DROUGHT, C., *Postgraduate Med. J.*, 1939, **15,** 258.

PERSONALITY, AND PAIN ASSESSMENT IN CHILDBIRTH OF MARRIED AND UNMARRIED MOTHERS

By

S. B. G. EYSENCK, Ph.D.

Institute of Psychiatry, University of London

Introduction

Studies which have investigated differences in pain tolerance between extraverts and introverts have reported that the former can tolerate pain better than the latter (Petrie, 1958; Poser, 1960). Nevertheless, behaviourly it was noticed that extraverts appear to complain of pain or discomfort readily and generally to "give voice" to their feelings more than introverts, who incline to "grin and bear it" and make light of past painful experiences. Furthermore, it has been shown in drug studies that subjects react differently to pain inflicted in a laboratory to that caused in other (i.e. natural) ways even if this be more severe (Beecher, 1957). It was therefore decided to investigate this discrepancy by testing subjects undergoing "natural", i.e. not experimentally inflicted, pain, and women in childbirth seemed a suitable group to approach.

Entering into the realm of obstetrics brought out a second point of interest for this project. It became obvious that obstetricians and midwives were unable to predict a woman's feelings and behaviour in the labour situation from her attitude at antenatal visits. This is partly because patients, at most antenatal clinics, are seen by a different doctor at each visit, and there is hardly time in the brief interviews for a predictive assessment of this kind to be formed. Nevertheless, general practitioners, who run district antenatal clinics and therefore see patients at each visit themselves (however briefly sometimes), find the same difficulty in making an accurate prediction of the patient's behaviour when she goes into labour. It seemed likely to us that the interviewers were concentrating on neuroticism as their criterion of "easy" or "hard" labours, this being discernible in terms of manifest anxiety, too many or too few questions about their pregnancy and labour, together with a general "worried" impression conveyed by the patient to the doctor.* Though this may be a variable of some importance, it seemed to us that more telling by far is the position of the patient on the extraversion-introversion continuum (Eysenck, 1957) and that some knowledge of this variable would allow the clinician a better prediction of the labour behaviour of his patient.

Finally, in testing mothers, several who were unmarried were seen and since they appeared to differ in their personality make-up somewhat, they were tested as a separate group and all results have been quoted for married and unmarried mothers separately.

* Stewart and Scott (1952) studied women in labour, giving interviews and Maudsley Medical Questionnaires to their subjects to ascertain whether the neurotic, tense women would be those likely to have "difficult" labours. They concluded that "Experience so far suggests that there is little if any relation between the behaviour in labour and the psychological assessment made during pregnancy. The great variability of behaviour suggests that a tense woman need not necessarily have a tense cervix or an abnormal labour." In later work, Scott and Thomson (1956) did report a tendency for the unstable women (as judged by interview and the Maudsley Medical Questionnaire) to have more difficult labours than the stabler ones.

Procedure

The writer tested one hundred mothers at the maternity wards of Lewisham General Hospital. Only primiparae and no Caesarean section or miscarriage patients were seen. Also, only English-born subjects were tested, partly to do justice to the vocabulary intelligence test used, and partly because foreign or Commonwealth attitudes and social mores (especially in respect to childbirth) differ so much from those in this country that it seemed unfair to mix the sample in this way.

Some unmarried mothers were seen at Lewisham General Hospital, but the majority, who came from Moral Welfare homes, were seen subsequently on their return after the confinement. To complete the sample of one hundred unmarried mothers, the writer tested at three Moral Welfare homes for unmarried mothers and their babies, and not all of these mothers were confined at Lewisham General Hospital.

The staff at the antenatal clinic of Lewisham General Hospital undertook to give out a questionnaire to all primiparae patients attending the clinic at the thirty-sixth week of pregnancy, and these forms (A.N. for Ante-Natal) were then placed into the patients' case papers, together with a brief questionnaire filled in by the doctor at this clinic, stating whether or not there was any *physical* abnormality which could cause the patient to have a difficult confinement. (Any such cases were excluded from our sample. There were, in fact, only three of these.)

The writer then extricated these papers from the case notes of the subject, together with a form filled in by the nurses present at the delivery of the patient, briefly assessing the behaviour of the patient during labour, listing drugs administered and length of labour. The patient was then seen for about twenty minutes, at any time convenient to the staff of the ward, during her ten days' or so stay in hospital.

First, the subjects were asked twelve questions on the P.N. (for Post-Natal) questionnaire, pertaining to the actual delivery, after which they were asked to rate, on a five-point scale, the *actual* pain they had felt during labour, taking the event all in all. Secondly, twenty-four extraversion and twenty-four neuroticism questions of the Maudsley Personality Inventory (Eysenck, 1959) were given, as well as twelve rigidity questions (Nigniewitzky, 1955). Finally, the Mill Hill Vocabulary Scale (Form I senior) set B was administered.

We thus had extraversion, neuroticism, rigidity and intelligence scores for all our subjects. In addition we had two measures of their pain in the labour situation:

1. The self-assessment, which was made from the following scale:

   (*a*) uncomfortable; (*b*) mildly painful; (*c*) painful; (*d*) very painful; (*e*) unbearable.

2. The Nurses' Ratings, which were made from the following scale:

   "During her labour, did your patient behave: (*a*) hysterically; (*b*) with great fear; (*c*) anxiously; (*d*) mildly anxiously; (*e*) calmly; (*f*) in perfect control?"

Since there was no opportunity of giving an A.N. form, or of obtaining Nurses' Ratings, on unmarried mothers not confined at Lewisham General Hospital, only the P.N. form and self-assessments could be quoted for this group.

Results

From the M.P.I., extraversion, neuroticism and rigidity scores for each subject were obtained. Their relative intelligence was computed from the Mill Hill Vocabulary Scale (Synonyms score); and their scores on Patient Ratings (self-assessment of pain in labour), Nurses' Ratings (Nurses' assessment of patients' behaviour during labour), and their ages were all tabulated. Finally the number of days after delivery that each subject was tested was also used as a measure to ascertain whether time elapsing after the event made any difference to their ratings or not. (There was in fact no relation with time passing as Table II will show.)

The means and standard deviations of the main scores are given in Table I, together with the critical ratio of the differences between married and unmarried mothers. The inter-correlations of the main variables were computed (Table II); Nurses' Ratings not being available, of course, for the unmarried mothers.

Table I

Means, Variances and Critical Ratios of Mean Differences

	Married Mothers N=100		Unmarried Mothers N=100		C.R.	Significant Level
	M	σ^2	M	σ^2		%
Extraversion (E) ..	29·8	84·86	32·4	79·17	2·03	5
Neuroticism (N) ..	15·6	92·92	25·8	119·43	7·00	0·1
Patient Ratings (P.R.) ..	2·9	1·16	3·1	1·47	1·23	N.S.
Nurses' Ratings (N.R.) ..	4·1	1·43	—	—	—	—
Rigidity (R)	11·0	20·16	11·6	18·35	0·97	N.S.
Synonyms (S)	16·5	24·11	14·7	15·86	2·85	1
Age (A)	25·2	23·50	19·5	20·35	8·61	0·1
No. days tested after delivery (No.)	3·7	6·74	21·9	188·76	13·02	0·1

Population Norms (N=1800) are: E=24·91; σ^2= 94·28
N=19·89; σ^2=121·44

Table II

Intercorrelations

Unmarried Mothers \ Married Mothers	E	N	R	S	A	P	NR	No. Days
E	( )	−·14	−·32‡	−·24*	−·06	−·37‡	−·16	—
N	−·24*	( )	+·35‡	−·00	−·01	−·19	+·09	—
R	−·40‡	+·29†	( )	−·23*	+·18	−·05	+·08	—
S	+·08	−·16	−·26†	( )	+·15	−·01	+·26†	—
A	−·04	−·02	−·02	+·32†	( )	−·14	+·10	—
P	−·38‡	+·09	+·31†	−·03	+·01	( )	+·30†	+·11
NR	—	—	—	—	—	—	( )	+·09
No. days	—	—	—	—	—	−·06	—	( )

* = significant at 5% level.
† = significant at 1% level.
‡ = significant at 1% level.

Each of the questions on A.N. and P.N. questionnaires respectively were analysed with respect to extraversion, neuroticism and pain-rating variables, and the *t* test results are listed in Tables IV and VI. Since these forms were of the Yes-No type, the *t* test was run by taking the extraversion scores of all those who endorsed the item against all those who negated it (leaving out don't know replies), and similarly with neuroticism and pain-ratings. We could, therefore, determine which of the items differentiated the groups with respect to the three variables we were interested in here. Again there were no A.N. data for the unmarried mothers who did not fill in this form before their delivery. It seemed of additional interest to record the percentage replies in the affirmative for each item (Tables V and VII), and to compare these for married and unmarried mothers. Finally, several chi-squareds were computed to emphasize the difference in extraversion and neuroticism, not only of the married from the unmarried mothers, but also of the mothers from the population means as given in the norms of the M.P.I. (Eysenck, 1959). (See Table III.) The scatter diagrams of extraversion against neuroticism for each group will help to illustrate the differences; Figures 1 and 2.

TABLE III

Chi-Squared: Extraversion and Neuroticism

	χ^2	Significant Level	N_1	N_2
Married mothers and population norms ..	86·987	0·1%	100	950
Unmarried mothers and population norms ..	106·977	0·1%	100	950
Married and unmarried mothers' samples ..	37·256	0·1%	100	100

TABLE IV

Ante-Natal Questionnaire Results

t-Tests for YES Against No Replies on the Following Items

	No.	t	Significant Level %	Question
(*a*) For Extraversion	13	2·319	5	"Do you worry a lot about what might happen during your confinement?"
(*b*) For Neuroticism	13	3·726	0·1	As above.
	15	2·259	5	"Does the sight of blood make you feel sick?"
	16	2·103	5	"When you experience pain of any kind, do you 'go to pieces' easily?"
(*c*) For Pain Ratings	3	2·342	5	"Did you stick to a special 'pregnancy diet'?"
	14	2·097	5	"Does pain at the dentist upset you very much?"

TABLE V

Percentage of Yes Replies to Questions in Table IV (A.N.)

Question	Percentage Yes Replies
3	27
13	29
14	34
15	17
16	10

TABLE VI

Post-Natal Questionnaire Results

t-Tests for YES Against No Replies on the Following Items

	Married Mothers			Unmarried Mothers			
	No.	t	Significant Level %	No.	t	Significant Level %	Question
(*a*) For Extraversion	3	2·694	1	3	2·686	1	"Would you say you had an easy labour?"
	6	2·906	1		—		"Were you ever, during labour, really afraid?"
	9	2·360	5		—		"Were there any events during the delivery that surprised you?"
(*b*) For Neuroticism		—		3	2·755	1	As above.
	6	5·192	0·1		—		As above.
	10	5·480	0·1		—		"Will you face a future pregnancy with some hesitancy?"
	11	3·088	1		—		"Would you say that at any time during your labour, you completely lost control?"
(*c*) For Pain Ratings	3	7·137	0·1	3	4·831	0·1	As above.
	6	3·281	1		—		As above.
	7	3·308	1	7	2·785	1	"Do you now think that having a baby is much easier than people make it out to be?"
	10	3·941	0·1	10	3·290	1	As above.
	11	4·738	0·1	11	3·243	1	As above.

TABLE VII

Percentage of Yes Replies to Questions in Table VI (P.N.); and Critical Ratio of Mean Differences Between Married and Unmarried Mothers

Question	Married Mothers Yes Replies %	Unmarried Mothers Yes Replies %	Critical Ratio	Significant Level	Question
3 ..	62	69	1·045	N.S.	As given in Table VI.
4 ..	41	21	3·175	1	"Do you consider that all you had heard about childbirth was in fact verified by your own experience?"
6 ..	22	23	0·169	N.S.	As given in Table VI.
7 ..	64	90	4·594	0·1%	As given in Table VI.
9 ..	33	20	2·107	5%	As given in Table VI.
10 ..	30	22	1·294	N.S.	As given in Table VI.
11 ..	30	23	1·125	N.S.	As given in Table VI.
12 ..	25	55	4·545	0·1%	"Do you now feel a bit despondent after it is all over?"

DISCUSSION

The first question we were interested in was that of the differential pain tolerance of extraverts and introverts. From Table II it will be seen that Extraversion and Patient Ratings (P.R.) correlate $-\cdot37$ in the married and $-\cdot38$ in the unmarried groups. Since the pain rating scale went from uncomfortable (score 5) to unbearable (score 1), the negative correlation we obtained means that the more extraverted the patient, the more unbearable did the labour situation seem to her in retrospect. Taking the Nurses' Ratings (N.R.) correlation with extraversion, however, it will be seen to be $-\cdot16$ which is not significant statistically, although it is in the same direction as the self rating. (Nurses' Ratings scale went from hysterically (score 1) to in perfect control (score 6).)

Neuroticism on the other hand, correlated $-\cdot19$ and $+\cdot09$ with pain ratings for married and unmarried mothers respectively, neither figures being significant. Nurses' Ratings turned out similarly non-significant at $+\cdot09$. Neuroticism, then, appears to enter into the picture very little, as against the influence of extraversion.

It will be further seen from Table II that most of the other variables did not influence the patients' pain ratings or those of the Nurses, except in two cases. First, there is a $+\cdot31$ correlation, in the unmarried mothers group only, between rigidity and pain ratings. However, when the influence of extraversion (quite highly correlated with rigidity; i.e. $-\cdot32$) is removed, the partial correlation drops to $+\cdot19$, which is not significant. Secondly, there appears to be a $+\cdot26$ correlation between intelligence and Nurses' Ratings, and this is quite interesting, because it suggests a tendency for nurses to judge the behaviour of their mothers in labour, in part by their intelligence, that is to say, by the ease with which they seem to follow instructions, etc.

The situation then, seems fairly clear on two counts. First, patients who maintain that their labours were very painful tend to be on the extraverted side, while those who make light of their experience incline towards the introverted end of the scale. It seems unlikely that extraverts should have *physically* harder labours than introverts, i.e. that they should be differentiated in terms of how

their babies position themselves in the uterus, or in their pelvic measurements, etc. The fact that extraverts express their labours as having been harder than do introverts suggests rather that they are the types, by and large, who are given to voicing their grievances, while introverts, with a life history of "keeping a stiff upper lip" and hiding their true feelings, are those who tend to play down the experience as not too painful. Extraverts, then, behaviourly *exaggerate* the painfulness of the situation, while introverts minimize it. This is an interesting finding, particularly in view of the experimental fact that introverts find pain *harder* to tolerate than do extraverts, thus suggesting that the exaggeration is indeed very gross.

It seemed possible that length of labour might affect the results in view of the build-up of reactive inhibition, particularly in the extraverted group (Eysenck, 1957). We consequently split our group (married mothers only because Nurses' Ratings were not available for unmarried mothers) into three; long, short and average labour times, and computed an F ratio of their respective extraversion scores, and this turned out to be non-significant. In other words, the length of labour did not differ for extraverts and introverts, which confirms that the intrinsic situation of childbirth is no different for extraverts and introverts, only their reactions to it because of their positions on this continuum.

Spontaneous and forceps delivery cases were kept separate in order to ascertain whether there were differences here, but none were found, so that the final computations were done with both groups combined. As might be expected, the only differences between mothers having their babies spontaneously and those requiring forceps help came from their ages, the forceps group being slightly older than the spontaneous group. (Age mean (married mothers) for the forceps group was 27·1, while that of the spontaneous group was 24·5.) However, age did not correlate with any other variable for the mothers (Table II), so that these differences were not relevant to our conclusions.

Secondly, as far as the Nurses' Ratings were concerned the situation is far less clear. Though the correlation of Nurses' Ratings with extraversion falls short of statistical significance, it is in the right direction, showing the tendency for nurses to notice the same trend as the patients themselves. Indeed the correlation between Patient and Nurses' Ratings was as high as +·30, which is significant at the 1 per cent. level (see Table II).

However, there were several difficulties we encountered here, administratively. First came the drug problem. Pethidine, Doriden and "gas and air" were given to the patients and naturally they were given different doses according to the length of labours and the general "need" for them as gauged by the nurses and midwives. Furthermore, it was impossible for nurses, who are already much overworked, to record their impressions at once (they have many more essential matters to record and see to at that moment, since in large wards like Lewisham labour ward it is not unusual for six or more babies to be born simultaneously!). Consequently the rating by the nurses was often done some time *after* the event (from memory) and even occasionally by other nurses, who had not themselves been present at the confinement, obtaining guidance from the case papers of the patient. We would, therefore expect that in a repetition of this kind of study, the Nurses' Ratings of the patients' behaviour would be more in line with the patients' own ratings, if it were possible to (*a*) control the drug intake of the subjects, and (*b*) obtain ratings by someone not engaged in other activities at the time who was concerned only with observing and rating the patients' behaviour in labour.

The application of our findings in this respect, seems to us to be that

patients ought to be given M.P.I. tests (especially noting extraversion scores) at one of their antenatal visits. Knowing the degree of extraversion of their patients might then help nurses to (*a*) drug extraverts more heavily than introverts and (*b*) make more nurses available for the former who tend to find the loneliness in the first stages of labour so much more intolerable than do the latter. In fact, experienced midwives appear to be able, instinctively, to pick out the "troublesome ones", i.e. those who are likely to be noisy or hysterical and disrupt the labour ward, making deliveries harder for others. Having decided that here they have a "difficult" case, midwives make their proper decisions as to drugs, etc. But probably they only identify the cases that will have a hard time in extremes; extraversion scores might help to get a broader classification perhaps.

This seemed to answer the second question we raised, which was the extent to which midwives and doctors could predict a woman's behaviour in labour from her attitude in antenatal interviews. This prediction, we feel, could be made more accurately when the concept of extraversion-introversion is included, it being doubtful whether neuroticism is involved to any great extent. We feel that intelligence is not really a factor here either (within normal limits), although we obtained a slight (−·24) correlation between intelligence and extraversion (Table II). This is probably because we used a vocabulary test of intelligence and this is known to give a slight bias in favour of introverts. When other tests of intelligence are included, this slight bias tends to cancel out and there are no longer any differences between them (Eysenck, 1947).

As a by-product to this investigation, very marked differences between married and unmarried mothers were observed. It will be seen from Table I that married mothers are more extraverted than the mean of the normal population (Eysenck, 1959); the critical ratios of the mean differences being 5·17 (significant at ·1 per cent. level) for extraversion and 4·45 (significant at ·1 per cent. level) for neuroticism. Also that unmarried mothers are even more so, having a slightly higher extraversion mean than the married group. The differences in neuroticism were even more marked, married mothers being *less* neurotic, on the whole, than the general population, while unmarried mothers are distinctly *more* so. Married and unmarried mothers did not differ in their rigidity and intelligence scores, but very much so in age.

When the extraversion and neuroticism scores of each group (married and unmarried mothers) are plotted (Figs. 1 and 2), it can be seen clearly that the main differences lie in two quadrants (low extraversion and low neuroticism, as well as high extraversion and high neuroticism). Very highly significant chi-squareds were obtained (Table III) when married and unmarried mothers respectively were compared with the general population norms, and when they were compared with each other.

In other words, though they do not differ in respect of intelligence and rigidity, unmarried mothers seem to be more extraverted and more neurotic than the general population, in addition to which they are far younger (as a group) than married mothers, when expecting their first baby (Table I). It is a little difficult to generalize too much from these figures, however, since all that can in fairness be said is that: unmarried mothers who go to institutions such as mother and baby homes (of the kind we tested in), tend to be extremely extraverted and/or neurotic. We do not know how many single girls have their babies at home, staying with their own parents, and whether their personality characteristics are similar to those we saw; nor can one tell how many girls have intercourse not resulting in illegitimate babies.

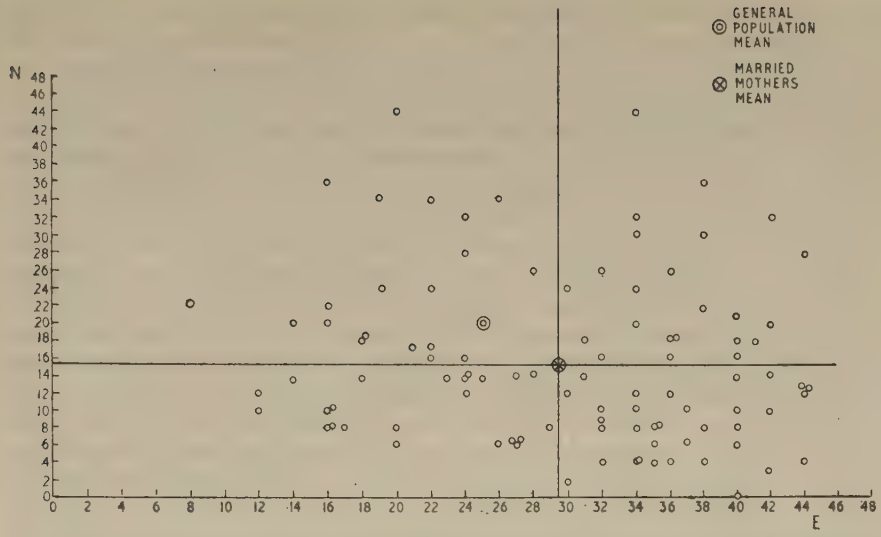


FIG. 1.—Scatter diagram of extraversion and neuroticism scores for married mothers.

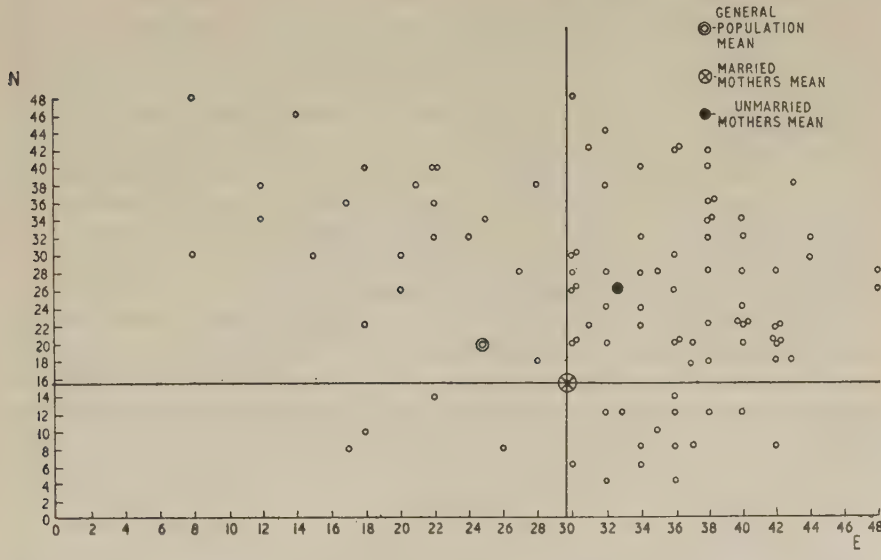


FIG. 2.—Scatter diagram of extraversion and neuroticism scores for unmarried mothers.

The results, however (taking the population sample we obtained), suggest that the girls who might be expected to become pregnant before marriage, would be those with high extraversion scores, or those with high neuroticism scores, or, most likely of all, those who score high on both. Girls who are sociable and mix easily and readily with people are more likely to meet many boys and go to parties, etc., where opportunities for intimacies could present themselves. Moreover, unstable girls might tend to look for security through

a boy friend, and be very amenable to persuasion through their fear of losing him. Doubtless when the two factors are fused, the likelihood of an early pregnancy is increased. It is perhaps worth suggesting here, that one other aspect of extraversion might be partly responsible for the illegitimate baby, and this is the lack of planning so characteristic of the extravert. It is not known, after all, how many introverts have intercourse before marriage but do not produce babies as a result, perhaps their capacity for looking ahead and planning being responsible.

There is a possibility that the high neuroticism scores of the unmarried mothers are slightly spurious. Certain items of the M.P.I. may measure temporary neurotic depression symptoms such as: "Do you ever feel 'just miserable', for no good reason?" or "Have you often lost sleep over your worries?" But there are other questions hardly relevant to their specific state of mind (due to their traumatic experience). It is thus possible that the neuroticism scores of these girls are somewhat inflated due to their recent "worry"; but this hardly accounts for their very much increased score over and above the general population mean. It would be interesting to give objective tests of neuroticism to unmarried mothers to see to what extent the M.P.I. still holds for people who have just experienced a major personal upset. One other thing suggests that the scores cannot be too erroneous. Not *all* the girls were highly neurotic; there were as many stable, but extraverted ones as there were unstable and introverted ones.*

At first the very gross age difference between our married and unmarried groups rather worried us, but Table II showed that very few items correlated with this variable of relevance to our study. The only significant correlation was between age (+·32, significant at the 1 per cent. level) and intelligence and this was found only in the unmarried mothers' group. This, we feel, is because they have not fully matured yet in intelligence, especially since this test was of the verbal kind. Table I shows a significant critical ratio between the groups for intelligence, which suggests that, when fully mature, the unmarried mothers would be of equal intelligence to the married ones. Pollock (1958) found that: "Social class, economic level and intelligence are not significant factors in the problem of unmarried motherhood."

Our picture of the unmarried mother as highly extraverted and/or neurotic seems to blend in well with impressions given by the staff of the Moral Welfare institutions we visited. They speak of the "really difficult girls" who moan and complain constantly, are very sociable (but often constitute a bad influence on the rest of the girls), hypochondriacal and generally create a trying atmosphere. We would expect this type of girl to be extremely extraverted and neurotic. In addition there are those who are very sociable and are keen to go out a great deal and at all times while, nevertheless, taking well to the rules of the institution and adapting well to any discipline imposed. These we would expect to be the stable extraverts. Finally, there are the quiet, broody introspective girls, who do not mix well and tend to "bottle up" their worries. They are regarded as somewhat atypical in these homes, and would seem to us to typify the neurotic introvert. Since only 4 per cent. of our total group were stable introverts they must be considered to be very much in the minority. (Half of

* Eilenberg (1960), studying married and unmarried mothers, noted this natural depressed and worried state in the latter group and commented that: "The clinical picture that emerges from the two groups is that the illicit group is characterized by a relative absence of previous mental illness associated with a minimal family history of psychiatric disorder; the pregnancy is unwanted and a temporal relationship exists between the pregnancy and the affective disorder. In effect the psychiatric illness is predominantly reactive."

these came from Moral Welfare homes, while the other half were seen at Lewisham General Hospital.)*

In addition to the M.P.I., from which extraversion, neuroticism and rigidity were scored, and the Mill Hill vocabulary test of intelligence, two forms were administered to ascertain some aspects of the patients' attitudes antenatally and postnatally. The A.N. form, which married mothers only completed at the thirty-sixth week of the pregnancy, comprised twenty questions on their attitude to their pregnancy and future delivery. The questionnaire was of the Yes-No type and *t*-tests on each item were computed for those saying yes against those saying no on extraversion, neuroticism and pain rating scores respectively. The results (Table IV) show that very few of the questions managed to differentiate the groups with respect to the variables mentioned and this may be either because we posed the wrong questions or because the subjects filled in their forms hastily at the antenatal clinic (probably in a hurry to get away home), and possibly several women discussed the items deciding collectively on the replies.

However, question 13: "Do you worry a lot about what might happen during your confinement?" gave a 5 per cent. level of significance differentiation on extraversion and a much clearer 1 per cent. level of significance one on neuroticism. Again, at the 5 per cent. level only, question 15: "Does the sight of blood make you feel sick?" and question 16: "When you experience pain of any kind, do you 'go to pieces' easily?" differentiated on the neuroticism variable. Question 3: "Did you stick to a special pregnancy diet?" and question 14: "Does pain at the dentist upset you very much?" differentiated between subjects who later gave high and low pain ratings. One is hesitant to interpret differences which are of such tenuous significance statistically, but inasmuch as they were found, tendencies might be noted for future work of this kind. For example, the result on question 3 suggests that those sticking to a special diet did, in fact, report less pain at their confinement. This, of course, might mean several things: (*a*) that the diet helped to produce an easier confinement; (*b*) that subjects having stuck to such a diet *believed* that it had made the confinement easier; (*c*) that the kind of person likely to have an easy confinement anyway is the type of person who is likely to adhere to diets and exercises during the pregnancy. It may be of interest here to note that (Table V) only 27 per cent. of the group endorsed this item, although there is some stress on diet in the antenatal care of the hospital.

Briefly then, though the results on this questionnaire were disappointing, it would seem that questions pertaining to worrying feature on the neuroticism variable, while those to do with pain attitudes differentiate subjects who later give high or low pain ratings of their confinement.

The P.N. questionnaire, administered after baby had been born, gave much more interesting results (Table VI). Question 3: "Would you say you had an easy labour?" differentiated extraverts from introverts and also, as might be expected, gave highly significant *t* results for pain ratings. In other words, extraverts said no to this question, as did those who rated their labour as painful. This result was confirmed in both married and unmarried mothers' groups, while with the latter neuroticism also plays a part in replying to this question.

* As a matter of interest a note was kept of which girls kept their babies and which formally agreed to adoptions. Their scores on extraversion, neuroticism, rigidity and intelligence were computed, but no significant differences were found. These variables, then, presumably do not influence the choice made by the unmarried mother as to the future of her baby.

Question 6, though extraversion was involved, clearly is mainly a matter of neuroticism, with a highly significant *t* obtained on this variable. (Unmarried mothers did not give significant differences on this question.) This question: "Were you ever, during labour, really afraid?" is one on which one would expect the neurotics (where worry and fear items usually receive affirmative replies) to differ, and where perhaps the extraverts feel it is part of the exaggeration of the labour situation. Similarly, those who scored high on the pain rating scale endorsed this question significantly more than those who scored low on pain ratings. (There is bound to be a certain amount of overlap here, of course, due to the correlation between extraversion and pain ratings; we felt, however, that it was worth while computing differences separately because the pain ratings score might give clearer differentiations on a questionnaire dealing mainly with pain or discomfort during labour.)

Question 7 gave some differentiation for both married and unmarried mothers on the pain ratings dimension only. ("Do you now think that having a baby is much easier than people make it out to be?") This, presumably, is just a matter of expecting a rather worse situation than they actually encountered, and this may well be why significantly more unmarried than married mothers endorsed this question (Table VII). This may tie up with the lower number of unmarried than married mothers who endorsed question 4: "Do you consider that all you have heard about childbirth was in fact verified by your own experience?" It suggests that unmarried mothers are more apprehensive of the delivery, and this may be because (being so young generally) they are much more ignorant of the procedure in childbirth. An effort is made, in the Moral Welfare homes in which these girls stay, to instruct them on mothercraft, etc., during their six weeks' stay before their babies arrive. On the other hand, there is probably another, much stronger influence coming from those girls who are back after their confinements, and who (being so predominantly extraverted) tend to exaggerate the horror of the event. This might account for the finding that unmarried mothers are surprised to find that what they had heard about childbirth (question 4) was not necessarily true, and are consequently of the opinion that having a baby is easier than people make it out to be (question 7). It seems a paradox that the girls speak of their own confinements as hard, yet are surprised that it was not as bad as others had made them expect!

Question 10: "Will you face a future pregnancy with some hesitancy?" gave significant differences for pain ratings in both groups and a very significant difference on neuroticism for married mothers only. As far as the former is concerned, the result is fairly clearly that those women who rated the event as painful were going to hesitate before starting a new pregnancy. But the interesting point to be made about this question is that although those who score high on neuroticism take note when they have had hard labours, and remember this when answering a question, such as this, about the future; there is no significance on the extraversion scale, which suggests that extraverts, though appearing to have had a hard labour, do *not* anticipate hesitation in starting another baby. (This confirms a lack of planning and learning from past experience which is also characteristic of extreme extraverts.)

Question 11: "Would you say that, at any time during your labour, you completely lost control?" gave differentiations on neuroticism and pain ratings. (The latter only for unmarried mothers.) Perhaps those who were high on neuroticism tended to really lose control at times, while extraverts exaggerate and verbally endorse that they lost control without necessarily having done so. At any rate, we do not place much confidence in this question as it stands, since

the wording caused some misunderstandings, some thinking that "losing consciousness" was meant by losing control.

Finally (Table VII), it might be of interest to note that a very significantly greater proportion of the unmarried than married mothers endorsed question 12, which was "Do you now feel a bit despondent after it is all over?" This may be due to the whole event seeming more undesirable for unmarried rather than married mothers. If it is true, as is sometimes maintained, that depressions or unpleasant events are forgotten rapidly, the above effect would be enhanced by the fact that unmarried mothers were seen very much later, after the birth, than were the married mothers (Table I). If the single girls had been seen straight after the births of their babies, even more of them might have been depressed than later.

The results on the P.N. form, then, suggest that extraverts, as compared with introverts, after the births of their babies, would be expected to hold the following attitudes about labour: (*a*) that it was not easy and (*b*) that they experienced moments of real fear during labour. Those women high on neuroticism would hold that (*a*) there were moments of fear during labour; (*b*) that they would hesitate before starting another pregnancy, and (*c*) that they thought they might have lost control during the delivery. For those women who considered their labours relatively painless, there was the additional belief that having a baby is easier than people make it out to be.

Summary

Though we have chosen a very complex problem to analyse, the results of the study appear fairly clear-cut. One hundred married and one hundred unmarried primiparae mothers were tested after the birth of their babies, and scores on extraversion, neuroticism, rigidity and intelligence were obtained, as well as replies to a postnatal questionnaire pertaining to their labours. In addition, married mothers completed an antenatal form at the thirty-sixth week of their pregnancy. The results show that:

(*a*) Extraverts tend to complain of more severe pain experiences during labour than do introverts.

(*b*) Neuroticism played no part in predicting either the behaviour or the attitude to labour of the mothers.

(*c*) Intelligence played no part in the patients' assessments of pain during labour.

(*d*) Married mothers had higher extraversion and lower neuroticism scores as compared to the general population means.

(*e*) Unmarried mothers tended to be more extraverted or more neurotic than the general population, the majority being both more extraverted and more neurotic.

Acknowledgments

The writer wishes to acknowledge the help and co-operation given by all the nurses and doctors of the maternity wards of Lewisham General Hospital. Particular thanks are due to Mr. Alistair Gunn, who enabled us to gain access to the wards and who showed much interest in our project and gave us the benefit of his advice. Also Sister Dalzell who helped so patiently in the various practical obstacles we encountered.

Many thanks also are due to the staff of the three Moral Welfare Church of England homes for unmarried mothers and their babies. Their hospitality and co-operation throughout was very much appreciated.

My thanks are due to my husband for constant help in this study, and to Dr. A. E. Maxwell for statistical advice.

Finally, the writer wishes to thank the Maudsley and Bethlem Royal Research Grants Committee for support in carrying out this investigation.

References

Beecher, H. K., "The measurement of pain", *Pharmacol. Rev.*, 1957, **9,** 59–209.

Eilenberg, M. D., "A prognostic study of neurotic pregnant patients—Preliminary Communication", *J. Ment. Sci.*, 1960, **106,** 1099–1104.

Eysenck, H. J., *Dimensions of Personality*, 1947. London: Routledge & Kegan Paul.

Idem, Dynamics of Anxiety and Hysteria, 1957. London: Routledge & Kegan Paul.

Idem, Das "Maudsley Personality Inventory" (M.P.I.), Göttingen. 1959. *Verlag für Psychologie.*

Nigniewitzky, K. D., "A statistical study of rigidity as a personality variable", 1955. M.A. Degree Thesis, University of London.

Petrie, Asenath, "Pain sensitivity, sensory deprivation and susceptibility to satiation", *Science*, 1958, **128,** 1431–1433.

Pollock, E., "An investigation into certain personality characteristics of unmarried mothers", *Dissertation Abstr.*, 1958, **18,** No. 6.

Poser, E. G., "Der figural After-Effekt als Persönlichkeitsmerkmal: Theorie und Methodik." Paper read at International Congress of Psychology at Bonn, 1960.

Scott, E. M., and Thomson, A. M., "A psychological investigation of primigravidae. IV—Psychological factors and the clinical phenomena of labour", *J. Obstet. Gynaec. Brit. Emp.*, 1956, **63,** 502–508.

Stewart, D. B., and Scott, E. M., "The assessment of efficiency in labour: psychological factors related to labour". The Transactions of the Edinburgh Obstetrical Society, Session CV., 1952–1953.

ASYMMETRY OF CEREBRAL FUNCTION*

By

WILLIAM GOODDY, M.D., F.R.C.P.

Physician

The National Hospital, Queen Square and

University College Hospital, London, W.C.1

It is the custom of our times to explain neurological, and, to some extent, psychiatric disorders by reference to a static or diagrammatic conception of the physiology of the nervous system, linked with the findings of morbid anatomy. But, in the words of Riese (1950), expressed in his *Principles of Neurology:*

> "Can the behaviour of a living organism be interpreted as purely mechanical? Though the organism remains submitted to the law of mechanics and physics, and though it is to the benefit of a steady improvement of our factual knowledge to explore the mechanics to the maximum possible, we must recognize that in a living organism mechanics are not left to themselves (which means to chance), but that they are at the service of a directing agency best described as the organism's welfare. The reflex must be conceived as an instrument of this agent. All disorders analysed and described in terms of reflex action are only instrumental ones. Neither the physician's task nor his possibilities extend beyond this limit. The directing forces of the organism will be withheld forever from the physician's acting power, if only for the reason that these forces are just ideas or principles of interpretation, but not perceptible realities."

Elsewhere in the same work, in one of his finest sentences, Riese criticizes the *mechanical restrictions* which present-day forms of study impose upon our attempts to *understand* the human organism:

> "It remains to be seen how long the self-inflicted limitation to purely instrumental activities and the neglect of man's free decision as an inner voice (not necessarily enunciated by man's acts) will stand the test of time and the unavoidable re-awakening of the individual; man experiences himself *primarily* as endowed with will-power and judgment rather than with pathways and nuclei."

It is the intention of this paper to outline (mainly in the classical manner which depends upon the concept of increasingly complex "levels" of performance of nervous tissue running parallel with progressive achievements of perception and volitional activity), certain notions derived from clinical experience about specialized functions; to consider the relation of such specialized functions to the form of the structures of the brain; to show the importance of the development of functions asymmetrically in structures which are themselves symmetrical.

As Riese says, and as we as ordinary citizens confirm, "Man experiences himself *primarily* as endowed with will-power and judgment rather than with pathways and nuclei." In health we think of ourselves as units, single persons. We express ourselves by the use of *personal* pronouns and adjectives (and, in fact, in all grammatical forms), so to give the effect of units. Thus we say, "We are human beings". "I am talking", "They are sitting down". We are aware of the parts of the body, which we can, for some chosen personal purpose, consider

* Substance of addresses delivered (*i*) 1958 to the Royal Medico-Psychological Association and (*ii*) 1959 to the Department of Psychiatry, University of Newcastle, at the invitation of Professor Martin Roth.

as units in themselves. We then say, "My right hand", "My left leg", "My eyes", and so on. But we still preserve the unit concept in the personal pronoun "My".

In some of the gravest forms of mental or nervous disease, we find, not that many forms of local disability are noted by the patient, but that, without special complaint of paralysis or sensory loss, the patient is no longer able to behave as an integrated unit. Because of defects of unitary function, usually labelled as defects of judgment, memory, behaviour, the patient is no longer able to adjust himself to living, and has to be specially cared for, on the grounds of "dementia" or "psychosis". Such patients are commonly found to have damage diffusely or heavily scattered through the substance of both halves of the brain. In head injury, metabolic, infective, arteriopathic, deficiency and drug-induced conditions and probably some psychiatric conditions, the patient loses his functional identity against the background of normal social activity, and is totally disabled.

Such a patient has sometimes lost his self-awareness and appreciation of himself as a single social entity to such a degree that he does not realize that his behaviour is not normal; nor that there is anything unusual in his being confined to the ward or even to a bed in a closed mental institution, such as a mental observation ward. He will be the last person to discuss the fact of his incontinence. He will not complain. If he has some vague notion that he is not free to go about his life normally, he will take no effective action to ensure an alteration of circumstances.

Between this state of total social disability, usually called "dementia", and the total performance of the person in full possession of mental and physical health, lie those disorders which occupy clinical neurology and psychiatry. For these two specifications there are fairly well-defined extremes of clinical categories; but at the "mental" end of neurology and the "physical" end of psychiatry there is no clear point of departure from one discipline to the other. The present paper, originating in neurological clinical material, deals with neurological symptoms and signs, even though it is fully realized that often in the "functional" disorders one may have to do with problems most suitably dealt with by psychiatrists.

We have now to study the following categories of disorder of cerebral function:

(*i*) Effects of damage to either of the brain hemispheres which are not side-specific.

(*ii*) Effects of damage to one or other cerebral hemisphere, which are side-specific:

(*a*) Signs of major hemisphere damage. Disorders of language.

(*b*) Signs of minor hemisphere damage. Disorders of spatial orientation.

I. Effects of Damage to Either of the Brain Hemispheres which are not Side-specific

Under this heading are those forms of simple hemiplegic signs which are found on the opposite side of the body from the side of the brain lesion, whichever side of the brain is damaged. These signs are, for many physicians and some neurologists, the only neurological evidence upon which they rely: but such signs, which are interesting, important and essential as a basis for clinical practice, are likely, as knowledge advances, to be regarded as an expression only of the most crude forms of dysfunction. They are sometimes absent even

at a late and disastrous stage of a nervous disease. Among such signs are gross alteration of behaviour, swelling of the optic discs, simple hemianopia, commonplace alterations of movement and sensation, changes in tendon reflexes and the plantar responses. Lesions producing these signs, and others of routine neurological testing, may be thought of as *situationally-specific in the antero-posterior axis of the hemisphere* (but not in the side-to-side axis of the hemisphere, that is, *not side-specific*).

From this statement there emerges, *per contra*, the suggestion that other categories (in the higher or more complex forms) of disorder will be determined by the side of the brain in which the accompanying lesion occurs. Such lesions are *side-specific about the longitudinal axis between the two hemispheres;* and at the same time, less situationally-specific antero-posteriorly than those causing the simpler manifestations of unilateral brain damage.

After this deliberately brief summary of the familiar signs of the non-side-specific effects of brain damage, we pass to the more complicated, more variable and less frequently studied matters of the *faculties in health*, and *symptoms and signs in disease*, which may be associated with specialization of brain function within each brain half.

The right and left cerebral hemispheres are *not anatomically differentiable, except for the feature of being mirror-images of each other*. That is to say, even the most expert neuro-anatomist cannot tell from a very thin vertical section of brain, whether he is looking at the front of a piece of right hemisphere or the back of a piece of left hemisphere. Yet it is our tradition to relate the establishment or possession of certain functions, such as *language*, with the "handedness" (in its broadest sense) of the person. One consequence of this idea is that, since (i) the left half-brain "controls" the right half of the body, and (ii) if what we call a right-handed person loses many of his language capabilities when he has left half-brain damage, therefore the left hemisphere is *responsible* for the maintenance of the language function. (Thus description conforms with current neurological parlance though it has been suggested (Gooddy, 1956) that some notions of cerebral localization and representation are not well founded.)

We determine a person's handedness by observing unilateral preferential use of either structure or function, after a careful survey of cultural and familial habits. But it is important not to forget that in all the activities which are used to signify handedness (writing, kicking, looking along a sight or optical tube) the whole body has to be stabilized; and often the other limbs and the trunk, as in writing or kicking, are essential for the complete act. Unilateral usage of a limb, with or as a tool, is forced upon the user because there is only one opportunity in action, though two structures or functions (left and right hands: left-handed and right-handed writing). Therefore the use of a single tool (e.g., pencil, monocular microscope) to achieve the passage of information, forces upon the person a form of competition between the left and the right. *The decision to use one side rather than the other implies the special training of the chosen side and the positive rejection of the other side*. This *selection* must have been contemporaneous with the earliest use of tools and the durable (written, painted, carved, inscribed) expression of language symbols. This neurological event, until very recently the most important evolutionary advance yet made, can be dated in the Sumerian era, about 4,000 years ago.

IIa. Language Testing and the Major Cerebral Hemisphere

Having determined handedness, we may apply tests to patients to see if the language faculty is disturbed. This subject is huge, for language includes

not only the spoken and written word, but also the symbol manipulation which underlies mathematics and the special languages of other branches of science, musical notation and other art forms, dance and mime, and simple gestures.

It is our custom to test first the patient's capacity to name objects. Though some authors state that nominal dysphasia signifies damage to the major temporo-parietal region, this not very discrete localization by no means always holds good. It is perhaps easier to agree with Goldstein, that nominal dysphasia is a sign of a fundamental change of behaviour. Loss of recall of names is often purely functional, and due to stress or tiredness. It is also a form of pure memory defect, and may be seen with diffuse brain damage alone. When we carry out tests for the expression and grammatical use of the various symbols with which the patient is familiar—and then the understanding of those symbols—we are in a better position to judge whether the lesion is anterior or posterior in the major hemisphere.

Simple Scheme for Language Testing

(*i*) The patient is asked to name up to 20 objects with which he is familiar. The name of the object and the patient's answer are written down by the observer.

(*ii*) The patient's *ability to express himself in spoken words* is judged from his conversation and his answers during history-taking.

(*iii*) The patient's *ability to express himself in written words and other symbols* can be judged from his letters or from a written specimen specially requested of him.

(*iv*) *The patient's ability to comprehend spoken words* can be tested by giving him instructions of increasing complexity.

(*v*) *The patient's ability to comprehend written words* and other symbols can be tested by giving him written instructions, in words or in other symbols with which he is familiar (e.g., mathematics, musical notation).

The clinical entities which many observers consider deserve the names of "apraxia" and "agnosia" will not be discussed here, for their nature is often difficult to define and their relationship to lesions inconsistent. Those readers who consider these conditions are associable with lesions in certain places, and also have side-specificity, have additional evidence of specialized functions derived from non-anatomically specialized structures.

IIb. Spatial Orientations and the Minor Cerebral Hemisphere

From a careful study of cases of unilateral brain damage (Gooddy and Reinhold, 1952, 1953) the writer believes it is fair to state that in the same way as we judge the major hemisphere essential for the control of language function, so we may judge the minor hemisphere essential for the perception and use of spatial information, underlying the faculty of spatial orientation. By spatial orientation is meant the person's capacity to relate:

(*i*) himself to extra-personal space;

(*ii*) one half of his body to the other; or one part of his body to another part;

(*iii*) various objects of extra-personal space one to another.

In disorders of these relationships we find geographical disturbances, so that the patient cannot use actual or mental maps and plans; he gets lost in

familiar surroundings. He cannot direct people in the street and may not be able to dress himself. He cannot make letters, designs and drawings, even though he knows what is wanted of him. This last disturbance may account for some cases of "constructional apraxia" associated with minor hemisphere lesions. Other complicated "agnosias", such as "autotopagnosia" (loss of awareness of relations of parts of the body to each other), or "prosopagnosia" (loss of recognition of faces), may also be found if the right tests are used.

Of particular importance in patients with minor hemisphere lesions is the investigation of their understanding or possession of what is commonly called the sense of direction. Thus many of them are unable to understand or draw a simple arrow form (Fig. 1).

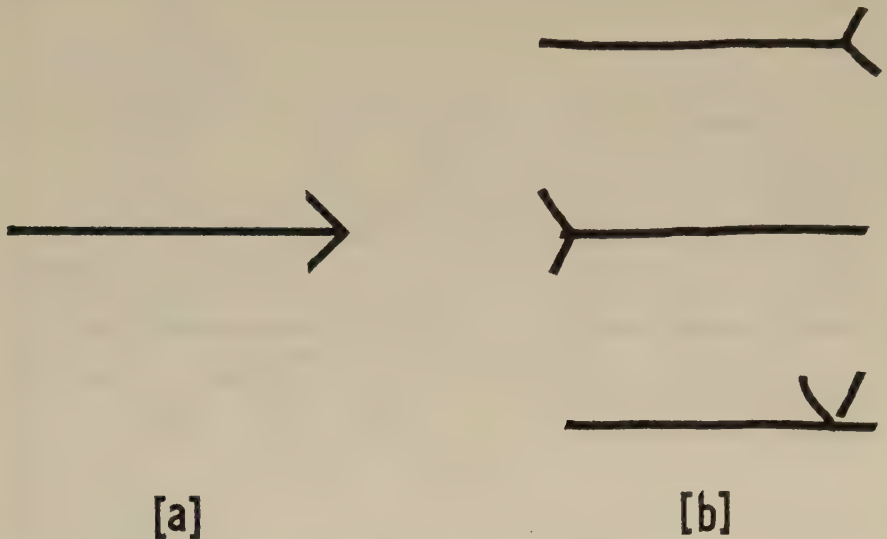


FIG. 1.—(*a*) Model for patient to copy. (*b*) Some abnormal arrow-forms drawn by patients with minor hemisphere disease.

It is implicit in the capacity to use space (*i*) to be able to *navigate* normally (which minor hemisphere damage patients cannot do) (*ii*) to have a proper awareness of the passage of personal and government time (Gooddy, 1958, 1959), because navigation is the accurate adjustment of space units to time units. The navigator in a ship or aeroplane says, "If I go in a certain direction (degrees and minutes of arc, indicated by a compass), for a certain time (indicated by a chronometer) at a certain rate (miles per hour, knots, etc., indicated by a tachometer) I shall arrive at X at noon". Human activity is identical in process, but achieved by the use of internal instruments. The well-known finger-nose test serves to illustrate the process of personal navigation; as do more obviously, walking, keeping appointments, writing, and all activities in which the body or its parts are in chosen places at the right time.

So far we have been considering matters generally familiar to advanced neurologists and psychiatrists, even though there may be some variation of opinion about details. We have found unequivocal evidence that *in, or by means of, identical-but-for-their-mirror-form hemispheres, damage to one will produce certain effects which are not seen when the other is damaged—that is to say, the achievement of localization of special functions in structures which are not themselves specially differentiated anatomically.* We find we are studying the effect

of asymmetrical function in symmetrical structures. According to communications engineers, "asymmetry conveys information". Dr. Robert Tschirgi, of the Department of Physiology, University of California, Los Angeles, first drew my attention to this concept. There is not space here to give detailed explanations and complicated examples, but the statement can be shown to be true. It may be understood by considering the number of items of information necessary for constructing a model from a pattern. For a rectangle of 9 squares, one needs to know only the size of one square. (Fig. 2a). For a plan composed of 9 squares arranged in a certain pattern, very numerous details are required (Fig. 2b). For a pattern of assorted shapes vastly more items of information are

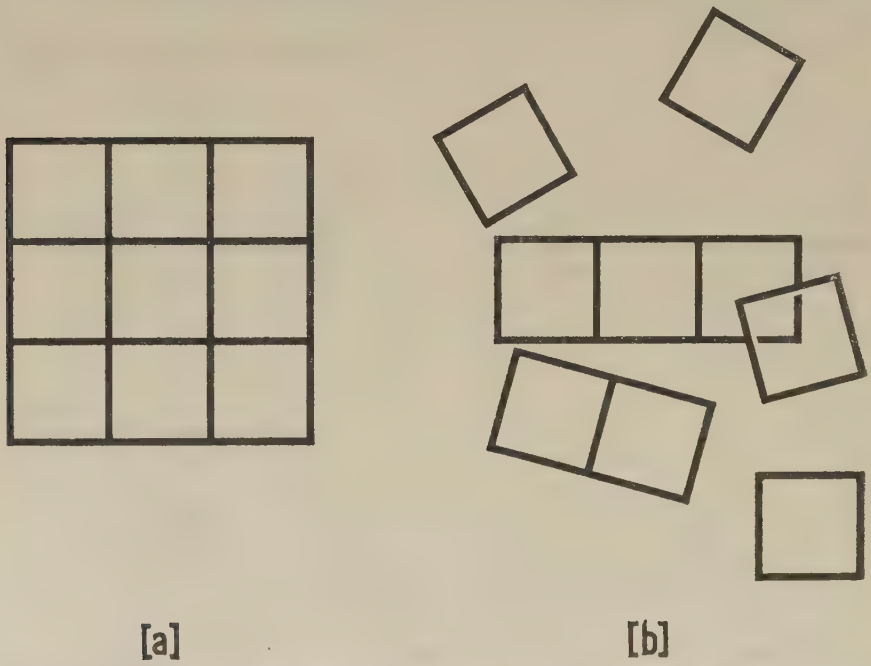


FIG. 2.—(*a*) Nine rectangles forming one larger rectangle. (*b*) Nine rectangles of same size and shape as in (*a*), but arranged asymmetrically. Very much more information of the relations of the rectangles is needed for reproduction of this pattern than for the reproduction of the pattern of (*a*).

required. If this theory is accepted, the human development of highly specialized functions of language and spatial orientation—the features by which we most clearly are superior to monkeys, dogs and birds and fishes—should be those which depend on the establishment of asymmetrical physiological mechanisms—even though we are still confined to the form of mirror-half-brains forced upon us by evolution.

Clinical studies have been providing the proof of this theory for the past hundred years.

There is other evidence of an attempt by the human being to escape from the limitations of anatomical structure, which require such immense periods of time for the evolution of new characteristics. We see in the ceaseless advances of scientific technology a process of extension of the range of human faculties. Perhaps the most important feature of such developments is the "building-in" of flexible time-range mechanisms into devices primarily designed for the

utilization of space. Such mechanisms vary from the simple and well-known to the very complex and abstruse. Examples are again to be seen in the development of language, by which a group or historical memory become available to any individual of a civilization. The general application of printing has had profound effects on everyday life; the effects of radio and television have yet to be calculated. Each of these technologies is a form of sensory extension, in the auditory and visual sphere in the macrocosm, comparable with the extension into the microcosm by the microscope and the electron microscope. Aviation technology now accurately extends the range of vision through distance, darkness and cloud, and enables the human operator to achieve miracles of navigation. The transistor valve begins to approximate to the neuronal unit of the nervous system. The electronic computer provides, in a time-compressed scale, results which obviate the similar more flexible but very slow processes of certain brain functions.

It is, in the writer's opinion, extremely important for the gap between neurology and technology to be closed; and it is right for the neurologist to be positive in proclaiming that studies of the nervous system in health and disease are fruitful means of improving existing scientific equipment, as well as being essential for the devising of new instruments (Gooddy, 1959). For however elaborate and intricate the new products of scientific technology, and whatever colossal purposes of exploration of space and time such vehicles and instruments subserve, they are created for but two purposes—that in whatever circumstances the human observer may find himself, he will be able to preserve the integrity of function of his brain stem (by which, finally, he keeps alive): and upon that living basis he will be able to perceive what there is to be known, and to use what he knows for his total welfare.

References

Gooddy, W., *Brain*, 1956, **79**, 167.
Idem, *Lancet*, 1958, *i*, 1139.
Idem, *ibid.*, 1959a, *ii*, 1155.
Idem, *J. Inst. Navigation*, 1959b, **12**, 3, 238.
Idem and Reinhold, M., *Brain*, 1952, **75**, 472.
Idem, *ibid.*, 1953, **76**, 337.
Riese, W., *Principles of Neurology*, 1950. New York.

NEURO-PHYSIOLOGY AND BEHAVIOUR DISORDERS IN EPILEPTIC CHILDREN*

By

EDWARD J. A. NUFFIELD, M.D., D.P.M.†

The Maudsley Hospital, London, S.E.5

Introduction

Consideration of the aetiology of behaviour disorders in epileptic children has been something of a test case in psychiatry: it divides sharply the "organicists" from the "environmentalists", while those absorbed in psychopathological theory are given free scope to describe the complexity of dynamic mechanisms without committing themselves as to the ultimate aetiological factors.

Thus L. Pierce Clark (1926), in describing various traits of the epileptic character, viz. egocentricity, hypersensitiveness, emotional poverty, and rigidity, calls this constellation "a singularly pure type of Narcissism". Although the explanation is along psychoanalytic lines, he believes that "the invariable character or epileptic make-up is a true stigma of the disease", thereby placing himself in the group of constitutionalists as far as aetiological theory is concerned.

The battle between "organicists" and "environmentalists" in this area mainly revolves around the question of whether the so-called epileptic personality really exists or is a sociological artifact. Most of the older continental literature affirms the existence of this entity and concerns itself with the description of its elements (Wallon, Minkowska, Mauz, Ssucharewa, Conrad and Stauder).

On the other hand other authors (Simma, Lindenberg, Hoff), consider that the cluster of traits labelled the epileptic personality is either rarely present or is the result of adverse social pressures. The work of Strotzka highlights the mother-child relationship as an aetiological factor (Werbenjak and Strotzka, 1953; Navratil and Strotzka, 1954).

American authors of psychoanalytic bent are mostly concerned with "explaining" the ictal event as a meaningful happening. This leads some authors (e.g. Heilbrunn) to deny any possibility of a neurophysiological basis for epileptic phenomena, whereas others (e.g. Gottschalk) leave room for the latter. Generally the formulation is something like that of Wayne Barker (1948): "The attacks are part of a mechanism of repression preventing unpleasant emotions, such as aggression, from disturbing the tranquillity of consciousness".

Similarly, Sperling (1953) considers that "the attacks represent a solution of a conflict, the conflict between extreme aggressiveness and extreme passivity". Interestingly enough, all these authors happen to describe the attacks of petit mal children; the characterological feature of this group will be referred to later. Most writers on behaviour disorders in epileptic children pay little attention to the question of the different types of epilepsy. Thus Bridge, in his textbook (*Epilepsy and Convulsive Disorders in Children*, 1949), failed to

* Abbreviated from part of an unpublished M.D. thesis.

† Present address: Royal Prince Alfred Hospital, Newtown, Australia.

separate his large and very interesting material into physiologically meaningful groups. Instead he drew up 5-point rating scales for the following factors: (*a*) heredity, (*b*) brain injury, (*c*) physiological disturbance, (*d*) personality disturbance, and (*e*) environmental fault. The only positive correlation found was between factors (*d*) and (*e*) ($r = +0 \cdot 673$). The other negative correlations do not, however, allow one to draw the conclusion that brain damage and physiological disturbance are irrelevant to any consideration of personality maladjustment or behaviour disorder in epileptic children.

The aetiological force of the environment has been underlined by the study of Grunberg and Pond (1957), which showed that a disturbed maternal attitude and breaks and changes in environment were particularly associated with conduct disorders (i.e. severe aggressive manifestation, truancy and wandering, lying and stealing). The authors matched two groups of epileptic children, with and without such conduct disorders, and investigated for presence of so-called organic, genetic, and social factors. The consideration of organic factors was purely on the history, i.e. whether a history of prenatal or postnatal damage, including meningitis and encephalitis, had been elicited. These factors, as well as the genetic ones (excluding a history of psychopathy in the family) appeared to be irrelevant. This particular study, however, focuses on only one aspect of the problem of environment and behaviour; it makes no attempt to separate out physiologically different groups.

Bradley (1951) attempts to make a sharp cleavage in the behavioural phenomena by dividing them into primary and secondary symptoms. There are five of the former: (1) erratic variability in mood and behaviour, (2) hypermotility, (3) irritability, (4) short, oscillating attention span, (5) selective difficulty in mathematics. The secondary symptoms are extremely protean: fear, resentment, despair, etc.

Bradley's primary symptoms are very similar to those attributed to brain damage in children generally; they lack specificity from the point of view of either epilepsy or of cerebral localization. The secondary symptoms are considered to be the child's reaction to his illness (i.e. specific to the child, non-specific as far as the illness is concerned). The division into primary and secondary symptoms seems artificial and unsound from a theoretical viewpoint. As Pond (1952) has pointed out, every symptom has a physiological basis and a psychological significance, and the interrelation of these two is too close to permit of any division.

Pond himself has attempted to relate electrophysiological data to the behavioural field (1955) and to apply the important findings of Hughlings Jackson, the Montreal School (Penfield and Jasper), Gastaut and his school, and the work of many others on cerebral localization, and the especial significance of the temporal lobe to the psychiatric aspects of childhood epilepsy. Originally (in 1952), he described three clear-cut clinical types "characteristic in aetiology, clinical picture, and outcome".

Group one is the petit mal children. Their personality is immature and over-dependent. They are nice-mannered, may be stubborn, but rarely aggressive; serious-minded and usually passive. The mothers seem reasonable on the surface, though rather anxious; they may nag a good deal. They inhibit their aggressiveness (Bidwell, 1952).

The second group is the grand mal child, with brain injury but no neurological deficit and of normal intelligence. These children are stockily-built and tend to be aggressive. The worst of them have temporal lobe foci and as a group they tend to have a bad family history and a bad environment.

The third group are the mentally defective epileptic children. Pond distinguished between two subgroups here: in the first mental defect and epilepsy are both due to severe pre-existing brain damage, while in the second mental defect appears secondary to severe ictal phenomena, prolonged confusional states, frequent grand mal, etc.

Somewhat parallel observations are made by Siegmund and Pache (1953) in a study of children with so-called pyknolepsy. The Bero test, a modification of the Rorschach, separated out two groups of children: the first showed "labile affect, basic anxiety and a friendly encounter". The second group displayed "perseveration, stickiness, and all the usual signs of the typically epileptic record". Physically these children resembled the athletic-viscous constitution of Kretschmer and Enke. Interestingly enough the second group tended to develop grand mal later on and responded poorly to tridione. Unfortunately EEG data are lacking. The authors speak of "neurotic" and "ictophil" components.

This differentiation is reminiscent of an account by St. Hildegard of Bingen (13th century) who described two types of individuals attacked by epilepsy (quoted by Temkin, *The Falling Sickness*, 1945): (1) the wrathful type who "when they fall to the ground they sometimes let forth a sound different from the natural voice" (i.e. the epileptic cry). (2) "People of unstable and easy morals." They have "an attractive look and gentle gestures: and while they too may emit a sound when falling down it is sad and natural". Even in those days there was a suggestion that different epileptic phenomena might be attached to people of different dispositions.

Returning to the present-day situation, it must be recognized that only a limited number of epileptic children will fall into one or other of Pond's categories (about 50 per cent. of his own sample (Pond, 1952)). In the rest a multitude of factors such as brain damage, I.Q. level, fit pattern and social situation operate, each varying independently and thus producing a most complex result.

It would appear to be of some interest to expand Pond's initial findings on the different varieties of epilepsy and to examine in greater detail the behaviour characteristics of different physiological groups. This is the purpose of the present study, which attempts to place previously reported behavioural differences on a quantitative and statistical basis.

The author had been interested in the studies on the behavioural effects of the rhinencephalon, commencing with Papez's theory of emotion and the early extirpation experiments of Kluver and Bucy (1939). Although subsequent work (vide Bard and Mountcastle, Spiegel, Miller and Oppenheimer, Schreiner and Kling, Kennard, Green and Arduini) showed the question to be a complex one and raised the possibility of there being more than one circuit involved, it did appear likely that the rhinencephalon was concerned with the expression of aggressive drive. From the experiments of Stoll, Ajmone-Marsan and Jasper (1951) one could deduce that an electrical disturbance in the temporal area meant that a corresponding disturbance in the rhinencephalon was present. One might expect from such evidence that children with temporal lobe epilepsy might show enhanced aggressivity.

On the other hand there is less known about the effect of areas involved in centrencephalic epilepsy (i.e. true petit mal) on behaviour as a whole. We know the anatomy of the region involved to a great extent (Jasper and Drooglever-Fortuyn, Hunter and Jasper, Ingvar), and that the brain stem reticular system has the function of arousing the cortex and maintaining wakefulness (Moruzzi

and Magoun, 1949). This however, does not by itself permit of any deduction regarding the inter-ictal behaviour of the petit mal child.

There is some evidence, however, that the spike and wave phenomenon is part of a homeostatic mechanism. Landolt (1956) has described cases whose mental state was normal when the EEG showed gross spike and wave, and who were mentally most disturbed when the EEG was normal. Hill *et al.* (1951) have shown that this mechanism was defective in some schizophrenics and Rowntree and Kay (1952) described marked fluctuations in convulsive threshold in catatonic schizophrenia; as the patients recovered the threshold dropped dramatically.

If the spike and wave phenomenon of central origin is a homeostatic phenomenon it may be possible to understand the personality of the petit mal child more easily. One might also speculate that the ready availability (for genetic reasons) of this response to stress makes psychological precipitation more feasible than in other types of epilepsy.

The present study seeks to delineate the behavioural correlates of the following groups of epileptic children:

(*a*) Those with rhinencephalic involvement.

(*b*) Those with centrencephalic involvement.

(*c*) Those with probably both.

(*d*) Those with neither.

The first two groups are those with temporal lobe foci and those with classical 3 c./sec. spike and wave. The third group is more problematical: but an approximation to it can be found by taking cases with irregular spike and wave or slow spike and wave (both generalized). According to Hill most of these have a primary cortical focus, frequently in the inferior frontal, medial temporal, or medial surface region, where a scalp recording is likely to miss them. Finally, the last group may be obtained by taking children with verified non-temporal convexity foci (i.e., frontal, central, parietal or occipital in location).

Regarding the behavioural phenomena, it will obviously be necessary to classify the data in some way. It will not be possible to consider all the behavioural disturbances, but a line of cleavage will be drawn between all aggressive manifestations and all anxiety or neurotic manifestations. A third group, comprised of stealing, wandering, truancy, arson, sexual disorders, will be considered separately. These three categories exclude a number of manifestations considered symptomatic, such as feeding disorders, gratification habits, enuresis, encopresis, etc. which are usually present in any diagnostic schema (vide Cameron, 1955), merely because their significance is too equivocal from the viewpoint of aggression *vs.* neuroticism. Nevertheless the three categories, while not absolutely comprehensive, comprise the majority of the usual "complaints" in child guidance practice.

The following predictions are made:

1. Children with temporal lobe foci are more aggressive than children with non-temporal cortical foci.
2. Children with 3 c./sec. spike and wave ("petit mal children") are more neurotic than children with non-temporal cortical foci.
3. Children with atypical or irregular spike and wave are intermediate, being more aggressive than the petit mal group and more neurotic than the temporal lobe group.

Material and Methods

The clinical material for this investigation was obtained from a pool of epileptic children investigated at the Maudsley Hospital, London, between 1947 and 1956. Three hundred and eighty children between the ages of one and 15 years were discovered from the records; in 322 of these adequate clinical and EEG data were available. This material has been described fully elsewhere, and the electro-clinical correlations discussed (Nuffield, in press). The sample was seen to be representative though biased in favour of the older age groups compared to material from paediatric sources. Because of this more accurate localization of the epileptic process was possible than in some series.

Various subgroups of the total sample have been reported elsewhere (Pond, 1952; Pond and Bidwell, 1954; Falconer and Pond, 1953; Grunberg and Pond, 1957) for different purposes. The function of the epileptic clinic where most of these cases were seen and investigated has been described before (Pond and Bidwell, 1954) and need not be outlined again. Naturally the gross incidence of behaviour disorders was high (59·6 per cent.); this figure is not comparable with those given by authors working with more or less unselected samples of epileptic children (Bridge, 9 per cent.; Chaptal *et al.*, 10 per cent.; Henderson, 12 per cent.).

The sex ratio of boys : girls was roughly 5 : 3. This was very much in line with ordinary child psychiatric experience. Thus of 233 new consecutive cases seen at the Maudsley Hospital Children's Out-patient Department 67 per cent. were boys.

The age distribution of the total group and the male and female subgroups is set out in histogram form in Figures 1, 1a and 1b.

The small representation of the younger age groups is particularly striking among the girls.

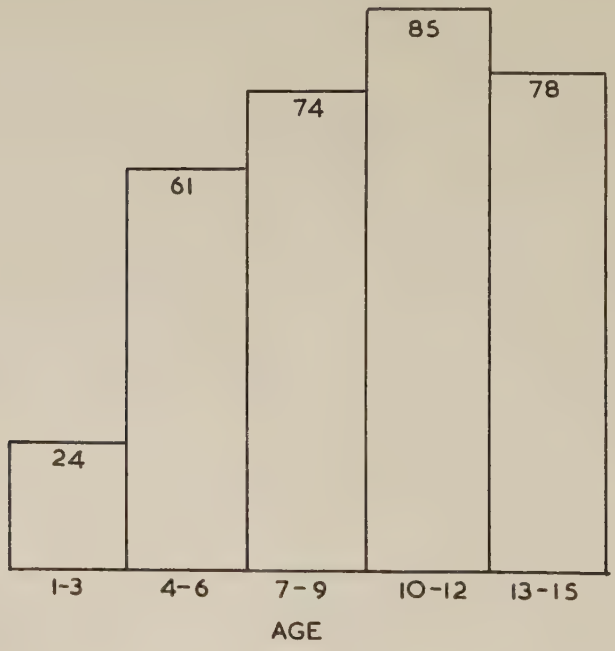


Fig. 1.

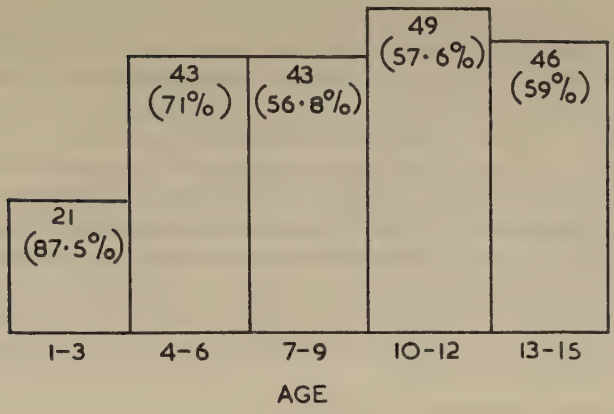


FIG. 1a.—Males.

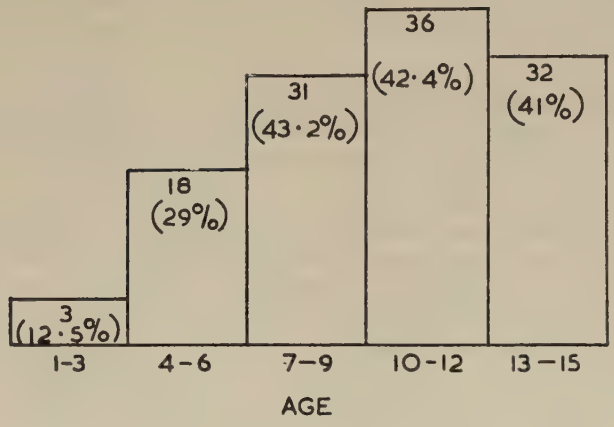


FIG. 1b.—Females.

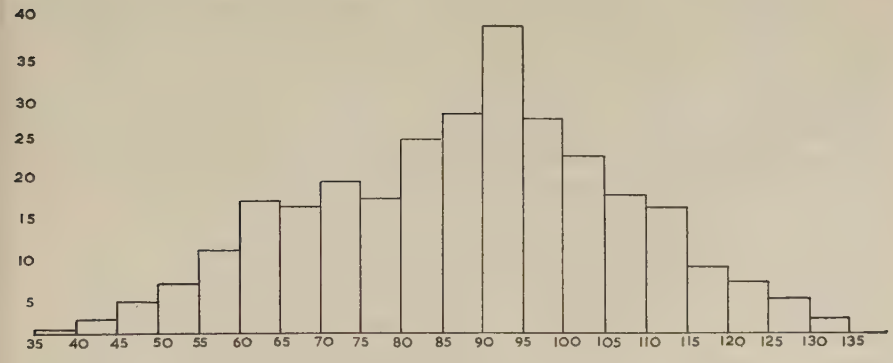


FIG. 2.

The next consideration is that of intelligence. Figures are available for 288 cases and are reproduced in Figure 2.

The mean I.Q. of the series was 89 with a standard error of 12. The mean I.Q. of 100 consecutive admissions to the children's out-patient department not suffering from epilepsy was 91, a very similar figure.

The socio-economic status of the epileptic group cannot be given in detail, but generally speaking it is fairly typical of a population attending a public hospital. The highest strata are somewhat under-represented.

Behaviour Ratings

In order to quantify the behavioural data along the above indicated dimensions, behaviour ratings were constructed for each case; it was possible to do this only because of the highly standardized way in which the psychiatric history had originally been obtained. This was according to Dr. Cameron's adaptation of Kanner's schema (*Child Psychiatry*, 1948). Part of the history is a systematic exploration of all areas of possible disturbances, called the Present Status. Two sections of this were of specific interest, viz. emotional habits and attitudes, and anti-social trends.

The following questions were extracted:

1. For aggression: (*a*) is he/she aggressive or submissive? (*b*) irritable? (*c*) stubborn? (*d*) a bully? (*e*) does he/she have temper tantrums? (*f*) is he/she destructive? (*g*) cruel to children and animals? (*h*) does he/she fight a lot? (*i*) is he/she bossy?
2. For neurotic manifestations: (*a*) is he/she timid? (*b*) sensitive? (*c*) unhappy? (*d*) has he/she any special fears? (*e*) nightmares, night terrors, or other attacks of anxiety? (*f*) does he/she cry easily? (*g*) fight his/her own battles?

Tension habits such as nail-biting or head scratching were also considered.

Positive answers were weighted according to the significance of the individual item—thus, being cruel to animals or children received a score of 3, being bossy only 1; anxiety attacks deserved a score of 3, whereas nail-biting got only 1. Wherever the informant has seriously modified a positive answer, the score for that item was halved.

In this way a maximum score of 20 on the "aggressivity" scale and a maximum of 12 on the neurotic scale was obtainable. This was called the number-of-symptoms score.

A separate score for aggressivity and neuroticism was obtained for each case by considering the present complaint; i.e. whether aggressive or neurotic symptoms were primarily complained of and to what extent and with what intensity. This was done along a 4-point scale (0–3). This meant, of course, that in over 40 per cent. of cases (where epilepsy only was the presenting complaint) this score was 0 for both variables. This 4-point scale alone did not yield data that could be handled statistically. A combination of the two scores was then effected for both aggressive and neurotic manifestations.

This was done in the following manner:

If score of 0 on intensity scale — final score 0 or 1 or 2 or 3
If score of 1 on intensity scale — final score 2 or 3 or 4 or 5
If score of 2 on intensity scale — final score 4 or 5 or 6 or 7
If score of 3 on intensity scale — final score 6 or 7 or 8 or 9

depending on which quartile the patient fell on the number-of-symptoms scale.

Each patient then had a final aggressivity (A) and neuroticism (N) score on a 10-point scale (0–9). In 300 of the total of 322 cases it was possible to allot these figures.

Turning to the anti-social conduct symptoms it was soon discovered that a similar procedure was not feasible because of the small number of items and

their comparative rarity. Disobedience and lying were omitted, because the former was considered too closely related to the aggressive traits and the latter because it has little significance from the child's point of view, merely underlining other symptoms in general (Holman, 1953). This left only 4 "symptoms": (*a*) stealing, (*b*) wandering and truanting, (*c*) fire-setting, and (*d*) sexual delinquency. Hence this group, i.e. non-aggressive anti-social conduct, was considered on a present-or-absent basis.

The behavioural ratings were done "blindly", i.e. without knowledge as to which physiological group the child belonged. It is not considered likely that at the time of history taking there would have been any awareness of the ultimate EEG classification.

The frequency distributions of A and N ratings are given in Figures 3 and 3a.

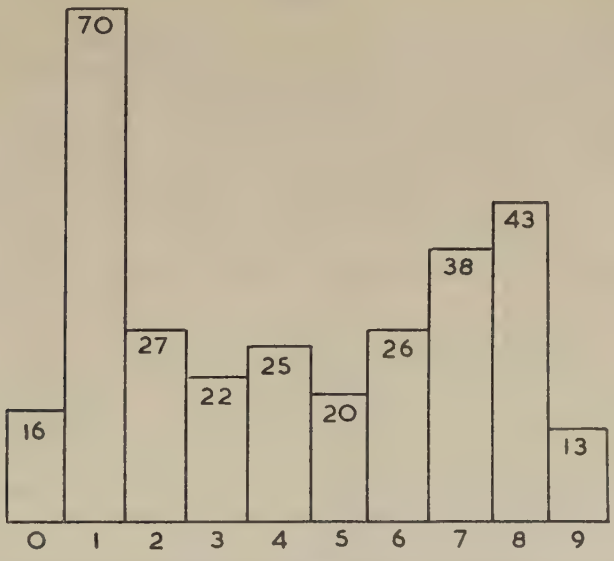


FIG. 3.—Distribution of ratings of "Aggressive Manifestations" (A ratings).

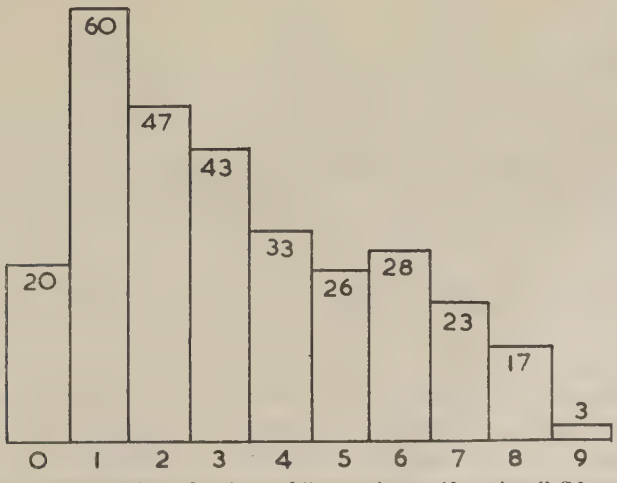


FIG. 3a.—Distribution of ratings of "neurotic manifestations" (N ratings).

It can be seen that the distribution curves are different and a theoretical "A" factor shows up more strongly than an "N" factor. The median of the A scale is 4, that of the N scale is 3. Altogether the comparison of the two histograms illustrates the fact that aggressive manifestations are more important and easier to plot than neurotic disturbances.

The question of the possible relationship between these A and N factors is investigated by Table I (V) which is a scattergram showing a wide spread of correlations.

The calculated value of r=—0·07, i.e. there is a quite negligible negative correlation between these two variables which can therefore be considered largely independent of each other.

TABLE I

		21	60	48	44	33	27	28	24	18	3	
	9	0	5	4	1	0	1	0	1	1	0	13
	8	5	7	10	5	4	5	2	2	2	1	43
	7	3	11	3	8	5	4	2	2	2	0	39
	6	4	5	5	4	3	1	2	2	0	0	26
A	5	0	3	0	5	4	3	2	2	1	0	20
	4	1	8	5	1	3	1	3	22	1	0	25
	3	1	1	3	3	1	2	6	4	3	0	24
	2	1	3	5	7	4	3	4	2	0	0	29
	1	6	15	10	6	7	5	7	5	8	1	70
	0	0	2	3	4	2	2	0	2	1	1	17
		0	1	2	3	4	5	6	7	8	9	

N

r=—0·07.

The total number of cases exhibiting non-aggressive anti-social disorders (A.S.) was 68, i.e. 21·1 per cent. of the total group. The relationship of this factor to the A and N factors was then investigated. This was done by taking 50 of the A.S. cases and matching them for age and sex with fifty cases without anti-social conduct (the last 18 of the A.S. cases could not be matched for age as no controls in the 13–15 age group were left over). As a result the anti-social conduct cases were somewhat more aggressive, the mean difference being 0·9. However, this is not significant statistically (t=1·87), the possibility of this difference appearing by chance being 1 in 13. Comparison of anti-social conduct cases and their controls for neuroticism showed the former to be a little less neurotic, the difference however being insignificant (t=1·02).

The sex ratio of boys : girls is 3 : 1 in the anti-social conduct groups,

showing a marked preponderance of boys. The age distribution is shown in Figure 4.

This should be compared with Figure 1 giving the age distribution of the total sample.

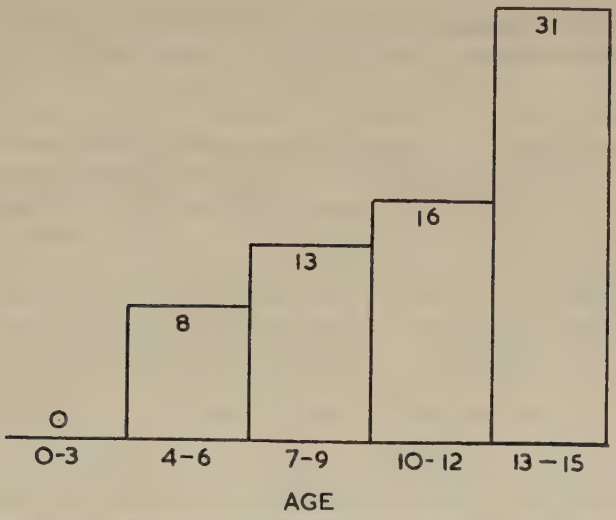


FIG. 4.—Age distribution of cases exhibiting anti-social conduct disorder.

EFFECT OF SEX, AGE AND I.Q. ON THE BEHAVIOUR RATINGS

It will be appropriate at this stage to consider the effect, if any, of such general factors as sex, age and I.Q. on the two behaviour ratings. It might be argued, for instance, that aggressivity is partly a function of maleness, neuroticism of femaleness, that aggressive manifestations predominate among the lower age groups and neurotic ones among the higher ages, that a low I.Q. will predispose to a high aggressivity rating and a high I.Q. to a high neurotic rating. These six hypotheses will be examined in series.

(a) *Sex*

Fifty boys were matched with fifty girls for age and intelligence, and their behaviour ratings compared. The boys were more aggressive than the girls, the mean difference of their ratings was 0·4, which was well below the ·1 level of significance (t=0·98). The girls were more neurotic than the boys, the mean difference being 0·5. This again was not significant statistically, level of significance being below the ·05 level (t=1·88).

(b) *Age*

To study the effect of age on the two behaviour ratings, the following table will be found helpful:

TABLE II

Age group ..	3–6 (63 cases)	7–9 (70 cases)	10–12 (85 cases)	13–15 (70 cases)
Mean A value	4·60±0·56	4·07±0·49	4·21±0·39	3·97±0·42
Mean N value	3·11±0·31	3·80±0·38	3·82±0·47	3·37±0·27

From this it can be seen that there is no consistent trend of either rating with increasing age, and none of the differences even approach statistical significance (the greatest, that between the N value of the 3–6 years old as against the 10–12 years old, has a t value of only 1·39 which falls well below the ·05 level).

It is reasonable to conclude from the above that age is not a prominent factor affecting the ratings.

(c) *Intelligence*

In order to assess the importance of this factor, 50 children with an I.Q. of 100 or more were matched for sex and age with 50 children with an I.Q. of 88 or less. The mean I.Q. of the whole group was $89 \pm 1 \cdot 2$, and the mode lies in the 90–95 range.

Comparison of the two groups (I.Q.=100+ *vs.* I.Q.=88−) shows that the low I.Q. children are slightly more aggressive, the mean difference being 0·5, and that there is absolutely no difference in their neurotic ratings ($\bar{0}=0$). The difference in their aggressivity is statistically insignificant (t=0·85).

In conclusion it can be said that none of the six hypotheses have been substantiated and five of them can be definitely rejected. There is a slight possibility that girls show a higher neurotic rating than boys and this will have to be borne in mind when discussing the neuroticism of different electrophysiological and clinical groups. As far as the effect of sex on aggressive rating and the effects of age and intelligence on both ratings are concerned, the null hypothesis still stands and it will not be necessary to match electrical and clinical groups for these variables before comparing them.

Correlation Between EEG and Behavioural Data

In order to obtain physiologically "pure" groups all cases falling into more than one EEG category have been eliminated, as have also those whose cortical foci were doubtful or failed to appear consistently. Also all cases where the I.Q. was less than 50 or who were under the chronological age of 3 were disregarded. This still left 233 cases and they were placed in 7 EEG groups: (1) temporal focus (T cases), (2) parietal or central, or occipital or frontal focus (PCOF cases), (3) 3 c./sec. spike and wave (hereafter called A cases), (4) irregular (and slow) spike and wave (hereafter called B cases), (5) diffuse spikes (called G cases), (6) non-specific abnormal (M cases), and (7) normal (N) cases.

The aggressivity (A) scores and the neuroticism (N) scores of these seven groups are given in Table III.

Table III

EEG Category	A Score	N Score	No. of Cases
Temporal focus	$6 \cdot 35 \pm 0 \cdot 35$	$2 \cdot 10 \pm 0 \cdot 22$	40
PCOF focus	$3 \cdot 80 \pm 0 \cdot 48$	$3 \cdot 00 \pm 0 \cdot 33$	30
3-second spike and wave ..	$1 \cdot 64 \pm 0 \cdot 31$	$4 \cdot 75 \pm 0 \cdot 59$	28
Irregular spike and wave ..	$4 \cdot 07 \pm 0 \cdot 44$	$4 \cdot 10 \pm 0 \cdot 39$	44
Diffuse spikes	$4 \cdot 53 \pm 0 \cdot 50$	$3 \cdot 25 \pm 0 \cdot 37$	32
Non-specific abnormal	$4 \cdot 40 \pm 0 \cdot 52$	$3 \cdot 58 \pm 0 \cdot 39$	33
Normal	$3 \cdot 73 \pm 0 \cdot 55$	$3 \cdot 73 \pm 0 \cdot 49$	29

The most striking feature is the high A score achieved by the temporal cases ($6 \cdot 35 \pm 0 \cdot 35$). This is paralleled by the remarkable low score on that rating that the 3/second spike and wave cases have. On the neurotic scale the positions are reversed: the 3/second spike and wave cases have the highest rating, the temporal cases the lowest. These two groups of cases seem to point to an inverse relationship between aggressive and neurotic manifestations, a relationship that did not appear in the whole epileptic group ($r = -0 \cdot 07$).

The position of the irregular spike and wave group is a more equivocal one. They combine a fairly "average" A rating with a rather high N rating. It is as if this series of cases were a mixture and could be further sorted out into cases properly belonging to the 3/second spike and wave group on the one hand, cortical groups including the temporal on the other. However, no further breakdown of these 44 cases could be justified on EEG or clinical grounds. It has already been mentioned that every attempt was made to search for cortical foci in this group; and in 13 cases where such foci were found behaviour ratings were available. The A rating was practically identical with that of the irregular spike and wave group without cortical foci ($4 \cdot 00 \pm 0 \cdot 78$ as compared to $4 \cdot 07 \pm 0 \cdot 44$), whereas the N rating was rather lower ($3 \cdot 30 \pm 0 \cdot 89$ compared to $4 \cdot 10 \pm 0 \cdot 39$). This difference is statistically quite insignificant (C.R. $= 0 \cdot 82$).

In order to assess more accurately the significance between the various means in Table III the t test was employed. This makes it possible to consider the relative levels of statistical significance ($\cdot 05$, $\cdot 02$, $\cdot 01$, $\cdot 001$ levels). To give an even more complete picture of the statistical analysis of the data, the actual t value will be quoted.

The figures of particular relevance to the hypotheses tested in this work have been underlined; they refer to the aggressivity of the temporal cases, the neuroticism of the 3/second spike and wave (A) cases, and both these features of the irregular spike and wave (B) group as compared to the PCOF group which has been erected as a control series. The particularly low aggressivity of the A cases and the low neuroticism of the T cases are features that have emerged and ensure that these two groups appear on opposite ends of both scales. The deviation from this hypothetical norm (the PCOF group) is more extreme for both groups on the A scale, the least significant deviation being that of the N score of the temporal cases ($p > \cdot 02$ only). This raises the possibility of the A scale being better constructed than the N scale. The significance of the difference in aggressivity between T and PCOF cases ($p = \cdot 001$) also appears to outstrip that of the difference between the neuroticism of the A and PCOF groups (P = only $< \cdot 01$), but the latter is still sufficiently large to command confidence. Furthermore differences between the aggressivity of T cases and such physiologically dubious groups as the normal (N) non-specifically abnormal (M) and diffuse (G) cases appear as significant whereas corresponding differences concerning the neuroticism of the A cases fall below any reasonable level of significance.

Table IV underlines the equivocal position of the irregular spike and wave (B) group. Referring back to the third hypothesis put forward at the end of the first part of this work, children in this group were expected to be more aggressive than the (A) group and more neurotic than the (B) group. These trends have been substantiated and the significance of the differences can be read from lines 7 and VII of Table IV. What is also of interest is to compare the B group with the so-called control group (PCOF). The difference in the neurotic score appears in line VIII and can be seen to be significant at the $\cdot 05$ level; the

difference between the aggressive scores (0·27, see Table III) is too insignificant (C.R.=0·41) to warrant inclusion in Table IV.

TABLE IV

	Difference Between	T Value t=	Significance p=
1	A score of T+A cases	10·15	<·001
2	A score of T+PCOF cases	4·72	<·001
3	A score of T+B cases	4·05	<·001
4	A score of T+N cases	3·67	<·001
5	A score of T+M cases	3·31	<·01
6	A score of T+G cases	3·20	<·01
7	A score of B+A cases	3·44	app. ·001
8	A score of PCOF+A cases	3·84	<·001
I	N score of A+PCOF cases	3·08	<·01
II	N score of A+T cases	4·86	<·001
III	N score of A+G cases	2·61	app. ·01
IV	N score of A+M cases	1·65	>·05 n.s.
V	N score of A+N cases	1·40	>·05 n.s.
VI	N score of A+B cases	1·00	>·05 n.s.
VII	N score of B+T cases	4·32	<·001
VIII	N score of B+PCOF cases	2·04	<·05
IX	N score of PCOF+T cases	2·44	<·02

T=temporal.
PCOF=non-temporal (parietal central, occipital, frontal).
A=3/second spike and wave.
B=irregular spike and wave.
G=diffuse.
N=normal.
M=non-specific abnormal.
n.s.=not significant.

Concerning the behavioural features of the B group, the following conclusions can be arrived at: (1) They lie intermediate between T and A cases as far as aggression is concerned. In this they are very similar to the central PCOF group. (2) As far as neuroticism is concerned they resemble the A cases rather closely and there is a strong suggestion that they are more neurotic than the neutral group (PCOF cases). (3) It is not possible to say at present whether their "normal" aggressivity is real or is being produced by putting together two physiologically distinct groups of children: one abnormally passive like the A children, the other with enhanced aggression like the T cases.

Little further can be said concerning the other three groups—i.e. the G, M and N cases which are physiologically doubtful and in whom one would not expect any definite behavioural trends. The figures in Table III just faintly suggest that these three categories are part of a continuum with the G cases towards the high A and low N value end, the N cases towards the low A and high N value extremity, the M cases fall in between. None of the individual differences are significant and they do not appear, therefore, in Table IV. It is tempting to suggest on physiological grounds that the cases with diffuse spikes (G) are likely to have some temporal lobe disturbance, and that cases with a

normal EEG are likely to have epilepsy of a centrencephalic or subcortical type, activation during recording having failed to arouse this system. However, the behavioural data are such as to support this assumption only in a very tentative manner.

Bearing in mind the findings concerning the effect of age, sex and I.Q. on the behavioural ratings as described in the previous section, these variables have been set out, as far as they concern the four chief EEG categories, in Table IV. Sex, age and I.Q. will be considered in their turn.

1. *Sex*

The greatest difference lies between the PCOF and B groups—19 : 11 as compared to 22 : 22. While the chi-square method shows this difference to be insignificant ($\chi^2=0{\cdot}84$), this relative preponderance of girls among the B cases tends to further reduce the significance of the enhanced neuroticism of the B group ($p<{\cdot}05$) remembering that girls as a group tend to have a slightly higher N score than boys (see above). The A cases also tend to have a somewhat greater proportion of girls, but the difference compared with PCOF cases is even less significant ($\chi^2=0{\cdot}42$, $p>{\cdot}1$) and the sex factor does not, therefore, explain the highly significant difference between the neuroticism of A and PCOF cases ($p<{\cdot}01$). The temporal (T) cases have a sex ratio practically identical with that of the "controls" (PCOF), and as the sex factor does not affect the aggressivity anyway, this need not be considered further.

2. *Age*

It is interesting to note that the T cases have the highest mean age, the PCOF cases the lowest. The difference between these two is quite significant (C.R.=3·38). None of the other differences are at all significant. From Table II one can see, however, that aggression is by no means related to greater age—rather the reverse. The 13–15 year olds are slightly less aggressive than the 4–6 year olds, the others being in between. It is therefore legitimate to conclude that the enhanced aggressivity of temporal cases is not a function of their age.

3. *I.Q.*

As with age there is no evidence that intelligence has played any part in these two behaviour ratings. There is a close concordance between the T, the PCOF, and the B groups. The mean of each of these is very similar to that of the epileptic group as a whole: $89\pm1{\cdot}2$. The A cases stand out from these: $100\pm3{\cdot}6$. They are significantly brighter than the PCOF group (C.R.=2·13) and even more significantly so than the T cases (C.R.=3·46). This finding is not surprising and most other authors have had the same experience with so-called petit mal children. As there is absolutely no effect of I.Q. on the neurotic rating, the high N score of the A group cannot be ascribed to their higher I.Q.

TABLE V

EEG Category	Boys	Girls	Mean Age (years)	Mean I.Q.
T cases	23	17	$10{\cdot}7\pm0{\cdot}43$	$84\pm2{\cdot}9$
PCOF	19	11	$8{\cdot}4\pm0{\cdot}55$	$89\pm3{\cdot}7$
A cases	15	13	$9{\cdot}8\pm0{\cdot}61$	$100\pm3{\cdot}6$
B cases	22	22	$9{\cdot}4\pm0{\cdot}61$	$85\pm2{\cdot}6$

In conclusion it can be said that statistical analysis of the behavioural data confirms the three hypotheses that this work seeks to prove:

1. Temporal lobe children are significantly more aggressive than "controls".

2. 3/second spike and wave children are significantly more neurotic than "controls".

3. Irregular spike and wave children are intermediate between the first two.

The only qualification one has to make is that the neuroticism of irregular spike and wave cases is much closer to that of 3/second spike and wave cases than that of temporal lobe cases.

Striking incidental findings were that the high aggressive score of temporal cases is accompanied by a remarkably low neurotic score, the reverse position obtaining in the 3/second spike and wave children. Since aggressive and neurotic manifestations do not correlate negatively in the series as a whole, it is tempting to suggest that in temporal lobe and 3/second spike and wave cases they provide alternative methods of discharge of emotional tension.

It now remains to look at the incidence of non-aggressive anti-social disorder among the various EEG categories. This has been set out in Table VI. The numbers are rather small, but suffice for statistical analysis by the chi-square method. As a result, only two differences were found to be significant: that between the T and the A cases ($\chi^2=6\cdot03$, $p<\cdot02$) and the B and the A cases ($\chi^2=4\cdot42$, $p<\cdot05$). The difference between T and PCOF cases was found to be insignificant ($\chi^2=2\cdot50$, $p>\cdot10$) and the other differences were of course even smaller; hence their significance did not have to be tested.

TABLE VI

Electrical Category	A.S. Present	A.S. Absent
T cases	12	28
PCOF cases	4	26
A cases	2	26
B cases	12	32
G cases	8	24
M cases	8	25
N cases	3	22

T=temporal focus.
PCOF=parietal, central, occipital or frontal focus.
A=3/second spike and wave.
B=irregular spike and wave.
G=diffuse spikes.
M=non-specific abnormal EEG.
N=normal EEG.
A.S.=anti-social conduct disorder.

When one considers that the A.S. manifestations occur much more frequently in the higher age groups (see Figure 4, page 9) and that the temporal cases have a higher mean age than the other groups (see Table V) the significance of the higher incidence of A.S. manifestations in the temporal group is further reduced and may well be accounted for simply by their age, seeing that the latter factor has an effect on the epileptic group as a whole as far as anti-social conduct disorders are concerned.

There is thus a marked contrast between the effect of physiological groupings on aggressive and neurotic scores on the one hand and the incidence of anti-social conduct (A.S.) on the other. There is a suggestion that the 3/second spike and wave children are rather "good" and the temporal lobe and irregular spike and wave cases have rather more frequent anti-social conduct disturbances than so-called control groups (PCOF cases especially), but this is only a trend and does not reach the statistical significance that allows one to assert a physiological factor in the incidence of this type of behaviour disorder with certainty.

Correlations Between Fit Pattern and Behavioural Data

An attempt was made to compare the aggressivity and neuroticism ratings of various clinical groups, bearing in mind that there would be considerable overlap of cases between clinical and EEG categories. (The extent of this overlap is reported elsewhere; *vide* Nuffield, in press.) The prediction is that the behavioural differences between clinical groups will be less clear-cut than those between EEG groups.

The clinical categories that have been selected as being of particular interest from the psychiatric angle are:

1. Temporal aura cases.
2. Non-temporal aura cases (visual, somatic sensory and some focal motor cases).
3. Grand mal cases (unassociated).
4. (*a*) Petit mal cases (alone).
   (*b*) Petit mal cases (total, i.e. alone and combined).
5. (*a*) Psychomotor cases (alone).
   (*b*) Psychomotor cases (total).

The results in Table VII have been set out as in Table III for the electrical categories.

A glance at the A scores shows that the temporal auras have a high figure, but that the psychomotor (total) group scores even higher. Petit mal cases score low, as expected. There is very little difference between grand mal cases and those with "non-temporal auras". The neurotic scores are more closely grouped together, the temporal aura and psychomotor cases scoring low while the petit mal cases are highest, but grand mal cases approach them closely.

Table VII sets out the significance of the various differences (−=alone, +=total).

Table VII

Clinical Category	A Score	N Score	No. of Cases
Temporal aura	5·15±0·43	2·85±0·30	45
"Non-temporal aura"	4·10±0·42	3·40±0·34	37
GM	4·40±0·39	4·14±0·32	56
PM (alone)	1·81±0·44	4·45±0·64	22
PM (total)	2·83±0·48	3·73±0·46	59
Psychomotor (alone)	4·24±0·70	3·00±0·42	17
Psychomotor (total)	5·30±0·64	3·28±0·40	46

The figures in Table VIII illustrate that, taking the 1 per cent. level as the critical point of significance, there are six significant differences among the A scores, but only one among the N scores. The figures underlined concern the aggressivity of the temporal aura group and the neuroticism of the petit mal group using non-temporal aura cases as the control group. Neither of these differences is statistically significant, so that the first two hypotheses work could not have been verified using purely clinical groupings.

TABLE VIII

	Difference Between	t=	p=
1	A score of T auras+petit mal (−)	4·94	<·001
2	A score of T auras+petit mal (+)	2·85	<·01
3	A score of T auras+non-T auras	1·73	<·05 n.s.
4	A score of psychomotor (−)+PM (−)	3·10	<·01
5	A score of psychomotor (+)+PM (+)	4·44	<·001
6	A score of petit mal (−)+GM	3·86	<·001
7	A score of non-T auras+petit mal (−)	3·57	app. ·001
8	A score of psychomotor (+)+non-T auras	2·00	app. ·05
I	N score of petit mal (−)+T auras	2·59	almost ·01
II	N score of petit mal (−)+non-T auras	1·55	<·05 n.s.
III	N score of petit mal (−)+psychomotor (−)	1·73	<·05 n.s.
IV	N score of GM+T auras	2·83	<·01
V	N score of GM+psychomotor (+)	1·94	almost ·05 n.s.
VI	N score of GM+non-T auras	1·47	<·05 n.s.

By using the grand mal group as analogous to the irregular spike and wave (B) group, it can be seen that they resemble the temporal aura cases closely in aggressivity, and the petit mal cases in neuroticism.

The psychomotor cases cause much confusion especially as there is a lot of difference between the unassociated and combined subgroups in their aggressivity. The former are intermediate in this regard, while the latter are even more aggressive than the temporal aura cases. This group cannot be contrasted with any electroencephalographic categories.

In order to compare the strength of association between electrical and behavioural data on the one hand, and clinical and behavioural data on the other, Table IX has been constructed. Here the temporal foci group has been treated as if analogous with the temporal auras, PCOF foci with non-temporal auras, the 3/second spike and wave group (A cases) with the petit mal (−) group, and the irregular spike and wave (B cases group) with the grand mal cases. The overall picture is that there are higher t values on the electrical side; in other words there seems to be a better spread of scores using electrical groupings. (In 5 cases no t value was given, in these cases the difference between the means was obviously insignificant.)

The only greater t value on the right hand side of the table is shown by the difference in aggressivity of grand mal and petit mal children which exceeds the difference in aggressivity between irregular spike and wave and classical 3/second spike and wave cases. The grand mal group is simply closer to the temporal group than the irregular spike and wave group.

TABLE IX

	Electro-behavioural Correlations	Clinico-behavioural Correlations
	T cases+PCOF cases	T auras+non-T auras
A score	t= 4·72 (p<·001)	t=1·73 (p>·05)
N score	t= 2·44 (p<·02)	t=? (p>·05)
	A cases+PCOF cases	Petit mal (−)+non-T auras
A score	t= 3·84 (p<·001)	t=3·54 (p=·001)
N score	t= 3·08 (p<·01)	t=1·55 (p>·05)
	B cases+PCOF cases	GM+non-T auras
A score	t=? (p>·05)	t=? (p>·05)
N score	t= 2·04 (p<·05)	t=1·47 (p>·05)
	T cases+A cases	T auras+petit mal (−)
A score	t=10·15 (p<·001)	t=4·94 (p<·001)
N score	t= 4·86 (p<·001)	t=2·59 (p<·02)
	T cases+B cases	T auras+GM
A score	t= 4·05 (p<·001)	t=? (p>·05)
N score	t= 4·32 (p<·001)	t=2·83 (p<·01)
	A cases+B cases	Petit mal (−)+GM
A score	t= 3·44 (p=·001)	t=3·86 (p<·001)
N score	t= 1·00 (p>·05)	t=? (p>·05)

In conclusion it can be said quite definitely that from the behavioural point of view electrical categories provide more clear-cut differences than clinical groupings based on the observable fit pattern. The distinction in aggressive and neurotic manifestations between temporal, non-temporal cortical and centrencephalic cases becomes blurred when these are translated into clinical terms. A further clarification of the behavioural pattern cannot be expected from a combination of EEG and clinical groupings, and especially in children, it seems most opportune to classify according to the electro-encephalographic picture which throws most light on the cerebral physiology as it is likely to affect behaviour.

THE ENVIRONMENTAL FACTOR

While a detailed study of environmental factors was the object of Grunberg and Pond's investigation, it was thought worth while to enquire whether the different physiological groups had been subjected to significantly different environmental pressures. Only a rough method was employed, all cases being rated as having either a good, fair, or bad environment. A bad environment was considered to be present, not only when such obvious factors as a broken home of gross material neglect was found, but also when a definitely pathological parent-child relationship had been discovered.

As a result of 321 cases (1 case could not be assessed), 121 (38 per cent.) were labelled as having a good environment, 36 (11 per cent.) a fair one, and 164 (51 per cent.) as having a bad one. The "fair" cases were kept to a minimum, being virtually those where there was some doubt as to the quality of the environment. They were virtually eliminated from further consideration.

The environmental situation among the four main physiological groups can be seen from the following table.

TABLE X

	Good Environment	Bad Environment
T cases	13	22
PCOF cases	12	15
A cases (3/second spike and wave) ..	10	13
B cases (irregular spike and wave) ..	15	20

While there is a slight suggestion that the temporal cases have the worst environment, none of the differences is statistically significant (between T and PCOF cases $\chi^2=0{\cdot}41$ ($p<{\cdot}05$) and between T and A cases $\chi^2=0{\cdot}27$ ($p<{\cdot}05$)).

These findings were a little surprising as we had been under an impression that cases of temporal lobe epilepsy were frequently saddled with the most adverse environmental factors. However, the crudity of the environmental ratings does not permit of any firm conclusions, and the findings certainly do not invalidate those of others who have pointed out the importance of environmental factors.

CONCLUSIONS AND SUMMARY

1. The question of behaviour disorders in epileptic children has usually been tackled without much attention being paid to the different neurophysiological patterns or the complexity of the behavioural picture.

2. It is necessary to consider epileptic children as falling into physiologically distinct groups, though the overlap is great and in many cases no adequate understanding of the underlying physiological disturbance is possible. This is largely due to the inadequacy of our present-day investigatory methods.

3. Nevertheless it is possible to isolate two subgroups in whom the rhinencephalic and the centrencephalic systems are primarily involved; these are the cases having temporal lobe foci on the one hand, or a 3 c./sec. spike and wave pattern on the other.

4. Clear behavioural differences between these two groups can be demonstrated: the temporal focus group shows a high incidence of aggressive manifestations and low neuroticism, while the reverse holds good for the 3 c./sec. spike and wave group (the "petit mal" group).

5. These differences are such that they clearly mark off the two groups from a "neutral" sample of cases consisting of non-temporal cortical foci (PCOF group).

6. Cases with irregular (generalized) spike and wave have been considered separately from the classical 3 c./sec. spike and wave group. The behavioural correlates of the former are such as to further justify this separation. These children are "average" in aggressivity and only a little more neurotic than the neutral control group. It may be that in a number of these cases both the rhinencephalic and the centrencephalic systems are involved. As these two systems seem to be associated with opposite behavioural features, the resultant picture may be expected to be somewhat indeterminate in character.

7. Other EEG groups were studied: those with a diffuse epileptic record, a non-specifically abnormal EEG, and a normal tracing. Of these the diffuse group were the most aggressive and the least neurotic, the normal the reverse, and the non-specifically abnormal in between. However, all the differences were very slight and could well have been due to chance.

8. Dividing the sample of epileptic children according to clinical fit pattern and comparing the behavioural features of the different subgroups yielded much less clear-cut a picture. It is clear that such a classification tends to place together cases whose underlying physiological processes are substantially different.

9. Regarding non-aggressive anti-social conduct disturbances the differences between the physiological groups are not so striking, though there is a suggestion that the "petit mal" children are rather "good" compared to temporal lobe children. Larger numbers are required for firm conclusions being drawn in this area of behaviour pathology.

10. The present investigation tends to support clinically the experimental evidence on the role of the rhinencephalon in facilitating aggressive behaviour. It is suggested that the findings on the centrencephalic groups lend support to the theory that the spike and wave phenomenon is part of a homeostatic mechanism.

11. The proposition that epileptic children with different underlying physiology exhibit different modes of behaviour appears to be strongly confirmed. It is concluded that while the environmental factors determine the presence or absence of behaviour disorders in epileptic children (pathogenic factor), the neurophysiological status determines the type and quality of the reaction (pathoplastic factor).

Acknowledgments

The work referred to was carried out while the author was on the staff of the Clinical Neurophysiology and Children's Departments of the Maudsley Hospital.

Thanks are due to Dr. D. A. Pond who gave consistent encouragement: also to Dr. J. D. N. Hill who advised on the neurophysiological aspects and Dr. K. Cameron whose advice on the behavioural aspects was similarly appreciated. Mr. A. D. Maxwell is to be thanked for assistance with the statistics.

Bibliography

Alstrom, C. H., "A Study of Epilepsy", *Acta. Psychiat. Scandin. Suppl.*, 1950, 63.
Arnold, O., *Wien. Z. Nervenheilk. u.d. Grenzgeb.*, 1954, **9**, 360.
Bard, P., and Mountcastle, V. B., *Res. Pub. Ass. Res. Nerv. and Ment. Dis.*, 1948, **27**, 362.
Barker, W., *Psychosom. Med.*, 1948, **10**, 73.
Idem, Burgwin, S., and Simons, D. J., *J. Nerv. Ment. Dis.*, 1950, **112**, 187.
Bidwell, B., *Ment. Hlth. (Lond.)*, 1952, **11**, 104.
Bradley, C., *J. Amer. Med. Ass.*, 1951, **146**, 436.
Bridge, E. M., *Epilepsy and Convulsive Disorders in Children*, 1949, New York: McGraw Hill.
Cameron, K., *Brit. J. Med. Psychol.*, 1955, **28**, 67.
Chaptal, J., Passouant, P., Jean, R., Campo-Bechard, C., Barjon, P., and Ribstein, M., *Pédiatrie*, 1953, **8**, 629.
Clark, L. P., *J. Nerv. Ment. Dis.*, 1926, **63**, 575.
Conrad, K., *Z. ges. Neurol. Psychiat.*, 1935, **153**, 271.
Idem, *ibid.*, 1936a, **155**, 254.
Idem, *ibid.*, 1936b, **155**, 509.
Idem, *ibid.*, 1938, **162**, 505.
Falconer, M. A., Hill, J. D., Meyer, A., Mitchell, W., and Pond, D. A., *Lancet*, 1955, **268**, 827.
Gastaut, H., *The Epilepsies*, 1954, Springfield, Illinois.
Gottschalk, L. A., *Arch. Neurol. Psychiat.*, 1953, **70**, 361.
Green, J. D., and Ardini, A. A., *J. Neurophysiol.*, 1954, **17**, 533.

GRUNBERG, F., and POND, D. A., *J. Neurol. Neurosurg. Psychiat.*, 1957, **20**, 65.
HEILBRUNN, G., *Psychoanal. Quart.*, **19**, 145.
HENDERSON, P. (1953), *Brit. J. Soc. Prev. Med.*, **7**, 9.
HILL, D. N., LOW, P. St. J., THEOBALD, J., and WADDELL, M., *J. Ment. Sci.*, 1951, **97**, 1.
HOFF, H., *Wien. Med. Wochenschr.*, 1953, **163**, 8.
HOLMAN, P., *J. Ment. Sci.*, 1953, **99**, 654.
HUNTER, J., and JASPER, H. H., *EEG Clin. Neurophysiol.*, 1949, **1**, 305.
INGVAR, D. H., *Act. Physiol. Scandin.*, 1955a, **33**, 137.
Idem, ibid., 1955b, **33**, 151.
Idem, ibid., 1955c, **33**, 169.
JASPER, H. H., and DROOGLEVER-FORTUYN, H., *Res. Pub. Ass. Res. Nerv. Ment. Dis.*, 1947, **26**, 272-298.
KANNER, L., *Child Psychiatry*, 1948, 2nd edition.
KENNARD, M. A., *J. Neurophysiol.*, 1955a, **18**, 159.
Idem, J. Nerv. Ment. Dis., 1955b, **121**, 34.
KLUVER, H., and BUGY, P. C., *Arch. Neurol. Psychiat.*, 1939, **42**, 979.
LINDENBERG, W., *Nervenarzt.*, 1951, **22**, 254.
MAUZ, F., *Zentr. Neurol.*, 1927, **45**, 833.
MINKOWSKA, F., *Ann. Méd.-Psychol.*, 1923, **81**, 149.
Idem, ibid., 1946, **104**, 321.
MORUZZI, G., and MAGOUN, H. W., *EEG Clin. Neurophysiol.*, 1949, **1**, 455.
NAVRATIL, L., and STROTZKA, H., *Wien. Z. Nervenheilk.*, 1953, **6**, 375.
NUFFIELD, E. J. A. (in press).
PAPEZ, J. Q., *Arch. Neurol. Psychiat.*, 1937, **38**, 725.
PENFIELD, W., and JASPER, H. H., *Epilepsy and the Functional Anatomy of the Human Brain*, 1954. London: Churchill & Sons.
POND, D. A., *J. Ment. Sci.*, 1952, **98**, 404.
Idem, Rec. Progr. Medicine, 1955, **19**, 329.
Idem, and BIDWELL, B., *Brit. Med. J.*, 1954, **2**, 1520.
ROWNTREE, D. W., and KAY, W. W., *J. Ment. Sci.*, 1952, **98**, 100.
SCHREINER, L., and KLING, A., *J. Neurophysiol.*, 1953, **16**, 643.
SIEGMUND, W., and PACHE, H. D., *Mschr. Kinderheilk.*, 1953, **101**, 191.
SIMMA, K., *Monatschr. Psychiat. Neurol.*, 1953, **125**, 683.
SPERLING, M., *Int. J. Psychoanal.*, 1953, **34**, 248.
SPIEGEL, E. A., MILLER, H. R., and OPPENHEIMER, M. J., *J. Neurophysiol.*, 1940, **3**, 538.
SSUCHAREWA, G. E., *Z. ges. Neurol. Psychiat.*, 1929, **123**, 626.
STAUDER, K. H., *Konstitution und Wesensveranderung der Epileptiker*. Leipzig: Thieme.
STOLL, J., AJMONE-MARSAN, C., and JASPER, H. H., *J. Neurophysiol.*, 1951, **14**, 305.
STROTZKA, H., *Mschr. Kinderheilk.*, 1954, **102**, 62.
TEMKIN, O., *The Falling Sickness: A History of Epilepsy from the Greeks to the Beginning of Modern Neurology*, 1945. Baltimore: Johns Hopkins Press.
WALLON, H., *J. Psychol.*, 1925, **22**, 500.
WERBENJAK, E., and STROTZKA, H., *Wien. Z. Nervenheilk.*, 1953, **6**, 375.

A CRITIQUE OF CURRENT VIEWS ON ACROCEPHALY AND RELATED CONDITIONS

By

L. CROME, M.R.C.P.E.

From the Neuropathology Department
The Fountain Hospital, London

Acrocephaly

Certain conditions associated with mental deficiency derive their name from some characteristic skeletal deformity. One of these is abnormal highheadedness or acrocephaly, a term often used interchangeably with oxycephaly, tower skull or turricephaly. To be sure, certain criteria have been recommended by some workers for confining each of the above terms to different sub-varieties of high-headedness and many alternative names have also been proposed (Günther 1941), but none of these have taken root. A distinction is made by many writers between acrocephaly and hypsocephaly or ordinary highheadedness: it is stated that the essential feature of acrocephaly is not highheadedness in itself but exaggerated upward pointing or angling of the head at some distance along its superior curvature so that, in theory, an acrocephalic head need not necessarily be hypsocephalic. However, it is doubtful if this distinction can always be sustained since many otherwise quite normal individuals have abnormal angling of the skull, while some recorded cases of acrocephaly presented a smooth and rounded profile of their upper cranial curvature in photographs and lateral skull X-rays.

Acrocephaly may be combined in recurrent patterns with other cranial and skeletal malformations to constitute acrocephalosyndactyly or Apert's syndrome and cranio-facial dysostosis or Crouzon's disease. These conditions are often discussed with other forms of cranial deformity (dysostosis), viz., hypertelorism, scaphocephaly, Franceschetti's syndrome or mandibulo-facial dysostosis, and the cleidocranial dysostosis of Marie and Sainton, although acrocephaly is an inconstant finding in these diseases.

A difficulty arises because some of the above terms are used in regard to people with no obvious disease but an anomaly of a particular physical measurement. Thus, it seems evident from the descriptions, and still more from the photographs, that the individuals with hypertelorism reported on by Günther (1934) and with Crouzon's syndrome (Günther, 1933) or the negro children with oddly shaped skulls described by Gordon (1958) as craniostenotic could hardly be regarded as examples of a pathological syndrome. On the other hand, the distinction between purely pathological syndromes and mere anthropological anomalies may be tenuous. It cannot be gainsaid, moreover, that the acrocephalic syndromes can manifest themselves incompletely.

This ambiguity weakens the generalizations of many authors and imperils simple comparison between different series. It will be pointed out below, for example, that it is still impossible to estimate even roughly the incidence of mental retardation among acrocephalic individuals. Precise information on certain crucial anatomical findings, such as patency or synostosis of some of the

cranial sutures, and on clinical signs, natural history and so on is also lacking. Moreover there is a need for additional quantitative data. Measurements are difficult to obtain and interpret because the pathological picture in each affected individual is made up of an inconstant number of variable deviations from the norm, some of which are slight and elusive (Grewel, 1948-49).

Acrocephalosyndactyly was first described as a separate disease by Apert (1906), following earlier publication of similar cases by different authors. In a recent study, Blank (1959 and 1960) found 88 recorded instances of the full disease and 41 of what he termed atypical acrocephalosyndactyly. He was also able to collect 37 new cases of the full and 14 of the "atypical" disease.

The cranial and skeletal features are striking. The skull is high and short antero-posteriorly. The eyes are prominent and widely set, sloping downwards and outwards in a so-called "anti-mongolian" slant. The palate is high and sometimes cleft showing in some cases a shelf-like osseous projection at the alveolar margin. The upper teeth are crowded. While the obvious abnormality of the hands and feet is syndactyly, the underlying skeletal dysplasia, well described by Valentin (1938) and Blank (1959), is in reality much more complex. In addition to the failure of some of the developing digits to separate transversely, there is frequent absence of the terminal phalanges (failure of vertical separation) and of some metacarpal and metatarsal bones. (Although this is the probable explanation of the digital deformities, another less likely one is secondary fusion of the phalanges.) The distal phalanges of the hands are often joined to each other by bony arches and may have a single common nail; this is particularly so in the case of the 3 middle fingers which usually form a "mid-digital mass". Visceral malformations occur frequently in the more seriously affected infants dying at or shortly after birth (Blank, 1960). An interesting change which has tended to be overlooked in the literature occurs in older patients. The digital bones acquire outgrowths projecting from the main body and this lends the phalanges a stellate appearance in radiographs (Valentin, 1938). This is reflected in limitation of joint movements.

Examination of the skull after death reveals very characteristic abnormalities in the shape of the bones, cranial fossae and calvarium. The details have been fully described by many authors (Greig, 1926; Günther, 1931) and need not all be recapitulated here: certain features pertinent to the present critique will be referred to below.

It is clear that the obvious change in the appearance of the patients must be paralleled by a greater or lesser deformity in the shape or size of most of the cranial bones and different authors ascribed, rather inconclusively, decisive significance to one or other of these bones or regions: some stressed changes in the vault and others at the base. For example, according to the recent observations of Kissel, Dureux and Tridon (1959) the principal deformity in the cranial dysostoses is at the base of the skull: brachybasia, shortening and exaggerated elevation of the anterior fossa, flattening of the orbits leading to exophthalmos, and increased distance between the lesser wings of the sphenoid causing hypertelorism. They thus feel able to characterize the cranio-facial dysostoses as "hypoplasia of the spheno-ethmoidal region".

The mobility of some of the larger joints, e.g., shoulders and elbows, may be impaired by flattening of the articular surfaces, epiphyseal fragmentation or ankylosis. The bodies and arches of some vertebrae are frequently fused or show deformities and outgrowths, while sacralization of the lower lumbar vertebra is common. Attention has been drawn by Wigert (1932) to the fact that acrocephalosyndactyly is a widespread skeletal dysplasia, the deformity of the

skull, fingers and toes being only its most conspicuous manifestation, while, as mentioned already, even more widespread malformations also occur in the more severe cases.

Besides those already mentioned, other noteworthy contributions on acrocephalosyndactyly include those of Davis (1915), Ruh (1916), Rieping (1919), Park and Powers (1920), Davis (1925), Weech (1927), Bronfenbrenner (1932), Ferriman (1941), Sirkin (1943-1944), Cohn (1945), Zellweger and Muralt (1952) and Gross (1957).

Cranio-facial dysostosis or *Crouzon's syndrome* (Crouzon, 1912 and 1929) is characterized by cranial and facial deformity which is essentially similar to that of Apert's syndrome. It has been said by those who distinguish between the two conditions that in Crouzon's disease the nose is more beaked or "parrot-shaped", the superior maxilla smaller, exophthalmos more common, and the mandible more prominent. But those differences are probably not real (Buckley and Yakovlev, 1948; Ferriman, 1941; and Schönenberg, 1958). It was also once held that Crouzon's disease was, unlike Apert's, hereditary, but a number of familial cases of Apert's disease and atypical acrocephalosyndactyly have now been recorded (Chotzen, 1932-33; Weech, 1927; Blank, 1959). A true distinction between the two conditions is, of course, the absence of syndactyly in Crouzon's syndrome, but this may be regarded as a sign of incomplete or atypical manifestation of acrocephalosyndactyly. Atkinson (1930) reviewed 86 cases of Crouzon's disease and 121 recorded cases had accumulated by 1948 when Eshbaugh (1948) reported a further example.

Blank (1959) divides all cases of acrocephalosyndactyly into two groups: (1) Apert's syndrome, as originally described, and (2) Atypical acrocephalosyndactyly. He uses very strict criteria for distinguishing between the two groups, placing, for example, cases with partial syndactyly, i.e., union of digits by soft tissue only, with the atypical instances of the disease.

Related conditions are often considered with those above under some common generic title such as cranial, facial or mandibulo-facial dysostosis, while other authors, laying stress on the presumed primary importance of premature synostosis, refer to the conditions as craniosynostosis or even craniostenosis.

Hypertelorism is characterized by excessive width in the spacing of the eyes. The great wings of the sphenoid are disproportionately small, and the small wings—large. The palate is high and narrow. Hypertelorism is very common in acrocephalic individuals, but may occur on its own. The original case described by Greig (1924) was in fact acrocephalic (or hypsocephalic). It is worth mentioning that the impression of increased interorbital distance is often not borne out by accurate measurements. *Scaphocephaly* or marked antero-posterior elongation of the head is, in the view of some workers, the result of premature synostosis of the sagittal suture. As pointed out by Park and Powers (1920), malformations of the extremities may also occur in cases of scaphocephaly. In another condition, the *Franceschetti* syndrome or mandibulo-facial dysostosis (Franceschetti and Klein, 1949; Weyers, 1951; Hövels, 1953) there is an "anti-mongolian" slant of the eyes, hypoplasia of the zygomata and mandible, malformation of the outer and, less frequently, the middle and inner ears, colobomata in the outer parts of the lower eyelids, a big mouth with a high palate, misplacement of the teeth and a blind fistula between the ears and mouth. A rare disease occasionally mentioned in relation to this group of conditions is the *cleidocranial dysostosis* of Marie and Sainton (Stewart, 1928-29).

It has been stated by Jaensch (1952) that transitional forms occur between

all of the above conditions. Hypertelorism in particular is, according to him, very common to them. It can be almost regarded as a constituent element of most of the cranial dysostoses. The relation of hypertelorism with the other dysostoses has been also considered by Zunin (1955).

Aetiology

Nothing certain is known about the aetiology of any of the above conditions and all the theories advanced by earlier workers have had to be abandoned for lack of evidence. These theories, enumerated by Günther (1931), include syphilis, rickets, birth injury, glandular disturbance, compression of the prechordal mesoderm by excessive flexion of the foetal head, non-specific meningitis, and so on. Blank (1959) concluded that typical acrocephalosyndactyly may be caused by a single gene in a heterozygous form and that mutation to this allele is correlated with increasing paternal age. Atypical acrocephalosyndactyly is, according to him, a heterogeneous collection of disorders, some of genetic origin. It is of interest that syndactyly is one of the malformations produced in the offspring of rats kept on a diet deficient in Vitamin B during gestation (Grainger, O'Dell and Hogan, 1954).

General Incidence

For reasons already outlined it is difficult to assess the incidence of the acrocephalic syndromes. Blank (1959 and 1960) estimates it at 1: 160,000 at birth for acrocephalosyndactyly and 1: 2,000,000 in the general population. He could make no reliable estimate for the atypical condition, but states that atypical acrocephalosyndactyly is even less frequently reported in the literature and in medical practice.

Pathogenesis

Apart from their general interest, the acrocephalic syndromes are of some practical importance: it is often asserted that early surgical treatment can obviate the danger of mental retardation and blindness in some cases. The view is based on the following theory of pathogenesis.

It is held that the cranial deformity results from the premature fusion (synostosis) of some of the sutures, the coronal in the case of acrocephaly and the sagittal in scaphocephaly. Bony growth in the direction perpendicular to the fused suture stops and the growing brain thereupon expands in the direction of the still patent sutures. This leads to the characteristic cranial deformity. It is further stated that cerebral growth in these abnormal conditions is accompanied by a rise in intracranial tension and this, in its turn, endangers the brain and the optic nerves. Hence it is recommended that the fused bones be redivided surgically, thus allowing the brain to expand more freely.

One of the main originators of the above theory was Rudolf Virchow (1852) who also suggested that the cause of the premature synostosis was local inflammation. It seems useful therefore to consider, as a background to the present critique, the following features of Virchow's thinking.

The first is his opposition to the various non-materialist trends of thought which prevailed before him and were still current in his lifetime (Rather, 1958). These included many "schools" and "systems" based on little more than speculation and tradition. Perhaps the chief weakness of non-materialist medicine in Virchow's time was its reliance on the so-called "natural-philo-

sophical method" ("Naturphilosophie") stemming largely from the teaching of Kant, which sought the answer to all biological problems in abstract thought. Having brought the microscope to the study of pathological processes, Virchow was in a position to base his views on the demonstration of material changes in diseased cells and organs, formulating later his classical cellular theory of pathology. The emphasis on local demonstrable change which could become irreversible and endanger the patient's life was incorporated in due course as a basic principle of pathology, especially surgical pathology. It may be said that Virchow's concepts were *par excellence* the ideology of surgery and have, as such, contributed greatly to the remarkable progress of that science in the ensuing century. By the same token, however, Virchow's tendency to oversimplify and to attach undue significance to localized events and mechanical causes has detracted from the usefulness of his concepts in the study of more complex non-surgical conditions. His attitude to cranial deformities is a good illustration of this point. The concept of their causation by localized inflammatory change and the subsequent abnormal moulding of the skull by mechanical forces is characteristically Virchowian. If true, his views would have clarified once and for all the aetiology and treatment of these conditions—surgical treatment; but, if false or only partially true, they could not stimulate further progress.

Secondly, Virchow was a lifelong enemy of racialism. A new feature of the racialist ideas circulating in 19th century Germany was the vigorous support given to them by some persons of academic standing, who tried to put the doctrine of racial superiority (or inferiority) on a "scientific" basis. One of their assertions was that the elongated skull found more commonly among the Northern Europeans was superior to the more rounded skull of the Slavs and Mongols. As an argument they used the association of low intelligence with roundheadedness in such conditions as acrocephaly and mongolism, which was then mistakenly regarded as a form of cretinism. Virchow refuted this argument by demonstrating that these conditions were not the expression, however extreme, of racial physical or mental characters, but the result of purely pathological processes, not specific to any race or people. While the details of his argument are no longer fully tenable, his insistence on the pathological nature of the extreme forms of cranial deformity, such as acrocephaly, remains, of course, perfectly valid. Moreover, his foresight in realizing the need for opposing racialism was confirmed a century later by the disasters which overtook his country and the world. A sinister detail of the Nazi legislation was the listing of acrocephalic individuals among those affected by the law "Zur Verhütung erbkranken Nachwuchses" (On the Prevention of Descendants with Hereditary Diseases) which was published before the mass murders in German and Austrian mental hospitals and old people's homes (Jensch, 1941-1942).

The Cranial Sutures in Acrocephaly

It is often taken for granted that the cranial sutures are always obliterated in acrocephaly. Blank (1959) states, for example, that normal suture markings are absent in all but the youngest cases of Apert's syndrome. The lambdoid, sagittal, coronal, metopic and squamous sutures, usually easily distinguishable in the crania of children and young adults, cannot be seen. A patent coronal suture was said by Jensch (1941–42) to have never been observed in any of the 82 cases reviewed by him. But this has not always been so in the experience of other workers. For example, the coronal suture was patent, but abnormally

situated, in a girl aged 1 year and 11 months presented by Carpenter (1910). A table showing the state of the sutures in 11 infants under 18 months reviewed by Park and Powers (1920) lists 3 as closed, one as patent, one as probably patent and 6 as having no record. In another series (Schönenburg, 1958), the coronal suture could be visualized radiologically in 7 of the 15 acrocephalic cases. In addition to the already discussed terminological ambiguity, the discrepancy may, perhaps, be also partly accounted for by the length of the coronal suture. A very short rudimentary suture is apparently often present as an extension of the lateral angle of the patent anterior fontanelle in cases showing an otherwise complete union of frontal and parietal bones (Gross, 1957).

While admitting its frequency, some workers are not prepared to attach decisive importance to premature synostosis. Günther (1931) and Greig (1924) regarded, for example, hypoplasia of the base of the skull as the primary abnormality, premature synostosis of the sutures in the cranial vault following, in their view, secondarily. Symptoms, if they occurred, were caused, according to Günther, by the narrowing of the foramina at the base of the skull and the resulting venous congestion. However, his observations have not been confirmed by other workers and it is difficult to see why, in the absence of conclusive evidence, an anomaly at the base should be preferred to that in the vault as the leading link in a long chain of abnormal events. It seems better to share Schönenburg's (1958) view, who regards premature synostosis as only one of the signs of widespread cranial dysplasia without any special pathogenetic significance. This view seems particularly reasonable since it has long been known that premature obliteration of sutures may be unassociated with any cranial deformity (Bolk, 1914–1915). Virchow's contention that synostosis leads to arrest of bone growth in a direction perpendicular to the fused suture has also been challenged on the basis of experimental study and growth measurements by Thoma (1924).

Many workers have discussed the way the synostosis comes about. Virchow's suggestion of an inflammatory origin has had to be abandoned. In the view of Rieping (1919), premature synostosis is the result of undue proximity to each other and to the coronal suture of the ossification centres in the frontal and parietal bones. Greig (1926 and 1935) believed that cranial sutures are not formed at all in such cases: the ossifying edges of the adjacent bones simply fuse with each other as soon as they come in contact. Greig (1926) distinguishes "true oxycephaly" in which there is complete obliteration of all cranial and facial sutures from "delayed oxycephaly" which is not congenital in origin and is never accompanied by exaggerated deformity or somatic defect. In a third group, "pseudo-oxycephaly" the synostosis is, according to him, limited to a few or even only one cranial suture while the facial sutures are never involved and the base of the skull is not affected. According to Eshbaugh (1948) and to Gross (1957) the continuity of the bones is not always the result of fusion; the bones may ossify *ab initio* from one common centre. Gross explains that the position of the missing suture is indicated in such cases by a bony ridge projecting to the interior of the skull.

In such discussions it is usually assumed that cranial bones grow mainly at their margin near to the suture lines but, according to Clark (1954), this may not be so.

It would thus seem that, pending further study, opinion on the constancy of premature synostosis and its significance in acrocephalic individuals must be reserved. Although frequent, premature synostosis is not invariable and is probably not the leading event in the development of this group of conditions.

Intracranial Pressure

The danger of rising intracranial pressure seems to have been reiterated from paper to paper and book to book without serious verification. Benda (1952) states, for example: "The first symptom is an increase in intracranial pressure which may be as high as 500 mm. of water; if the discrepancy between brain thrust and bony resistance is too great, children die from brain pressure." In fact, however, the C.S.F. pressures appear to have been seldom measured. It is true that workers, particularly surgeons, have reported elevated pressures in some of their, presumably selected, cases (Laitinen and Sulamaa, 1954–55; Laitinen, 1956). In most other records, C.S.F. readings were, if mentioned, well within normal limits (Bussola, 1928; Wigert, 1932). It is moreover difficult to understand how pressures of the order mentioned by Benda (1952) can be compatible with prolonged survival and not result in a wide separation of the still patent sutures in the manner familiar in cases of obstructive hydrocephalus. It is also unlikely that excessive pressure could, if prolonged, fail to produce progressive mental and physical deterioration, the absence of which in acrocephalic individuals has already been noted.

"Digital" Impressions of the Skull

An interesting and very common accompaniment of acrocephaly is the occurrence of "digital marking" or "copper-beaten" appearance in skull radiographs. Post-mortem examination of the affected skulls shows corresponding areas of bone wasting or cranio-lacunation. In fact, some of these laminae contain no bone at all, consisting merely of soft tissue which disappears entirely if the skull is macerated after death (i.e., immersed in water until complete disintegration of the soft tissues occurs). The brain may even herniate through one of the holes, as in a case presented by Gross (1957), but it is not clear from his report whether the hernia was congenital or not.

The digital markings are usually taken as evidence of raised intracranial pressure; they are held to follow upon the excessive pressure or pulsation exerted by the contiguous cerebral convolutions. However, there have also been dissenting opinions. Digital impressions in infants, as contrasted with adults, may not always be caused by raised pressure according to Jensch (1941–42). Weigandt (1921) went so far as to deny that digital impressions corresponded to the pattern of cerebral convolutions, i.e., that they were gyral imprints. This particular objection appears to be unfounded. There are many statements in other reports testifying to correspondence between gyri and digital impressions. This was so in a case at the Fountain Hospital, also mentioned below, where the skull was removed at autopsy and macerated. Careful matching with the fixed brain of this case confirmed that the digital impressions and perforations (lacunae) were true imprints of the cerebral convolutions. It does not follow, however, that the digital impressions, even if true imprints of gyri, are necessarily produced by elevated pressure. It is noteworthy that no histological evidence of bone resorption, such as might be expected if the thinning of the bone were due to pressure erosion, was found by Candreviotis (1955) in cases of spina bifida—another condition often associated with digital impressions. In the histological examination of the bones in a case of oxycephaly (Howkins, Jefferiss and Handley, 1938) there was also no evidence of bone resorption. The authors consider that the pathological material indicated "disorganization in bone growth and joint formation". Schönenburg (1958) suggests that the impressions in acrocephaly are only one manifestation of a general dysplasia,

and this appears to be the most reasonable view in the present state of knowledge.

What has not been hitherto stressed in published reports is the obverse process—overgrowth or excessive relief of the bone upon the interior of the skull in at least some cases. This presents either as exaggeration of the normally present ridges and elevations or as new structures (Eshbaugh, 1948). It is difficult to conceive of this appearance as a result of simple intracranial hypertension; it certainly does not occur in established cases with high intracranial pressure, whether accompanied by a lacunation or not. (Greig (1926) states, however, that the inner table of the cranium is smooth in "true oxycephaly" in contrast to its roughness in "false oxycephaly".)

It should also be noted that digital impressions have been observed and recorded in some of the youngest acrocephalic infants. Thus, if produced by raised pressure, this must happen antenatally.

Optic Atrophy

Like the "digital impressions", optic atrophy is often cited as evidence of rising intracranial pressure. The finding of optic atrophy in acrocephalic individuals was being reported even before Apert's publication (Uhthoff, 1905) and early workers believed it to be very common (Dorfmann, 1908). According to Fletcher (1911) impairment of vision and optic atrophy were "almost invariable in this condition". These very high estimates have declined in the course of years: Jensch (1941–42), for example, put it at 12·2 per cent in his series of avowedly severe instances of acrocephaly, all in mental hospitals. Blank (1959) gives no estimate of optic atrophy, but he could find no instance of blindness among his cases. It is possible that the anomaly of the optic discs when observed in acrocephaly tended to be diagnosed as optic atrophy secondary to raised intracranial pressure because this is what was expected to happen.

Many acrocephalics are mentally defective and mental defectives often have encephalopathies associated with smallness and other anomalies of the optic nerve; these are relatively seldom caused by raised intracranial pressure, being usually a manifestation of widespread neural dysplasia. This may well be so in acrocephaly. Blank (1959) quotes a number of cases of acrocephalosyndactyly in whom the C.S.F. pressure was quite normal in spite of an existing disc anomaly. He does not think raised intracranial pressure is responsible for the "optic atrophy". This is in accord with the views of Kissel, Dureux and Tridon (1959) who are also dissatisfied with the mechanical explanation of the ocular anomalies in the cranio-facial dysostoses and draw attention to the fact that many of the reported ocular anomalies were in fact true malformations.

In considering possible causes of optic nerve changes and failing vision, it is necessary to bear in mind the exophthalmos due to the flattened orbits. This may lead in severe cases to dislocation, corneal ulceration and other damage to the eyeball (Sherne, 1938). The failing vision in a case reported recently by Kahn and Fulmer (1955) may have also been caused in this way, since the patient had exophthalmos, bilateral keratotonus and rupture of one cornea.

Following upon an earlier, rather casual, suggestion of Greig (1926), another mechanical explanation of "optic atrophy" has been recently offered by Gross (1957). He suggests that the foreshortening of the skull and its upward distortion lead to an exaggeration of the usual upward convexity and basal concavity of the cerebral hemisphere—"cerebral kyphosis". As a result, the diencephalic structures are lifted off the base of the skull, the basal cisterns are

deepened and the structures traversing them are displaced upward at their cranial attachment. The optic nerves are thereby stretched and abnormally angled as they emerge from the optic canals. It is this stretching and rubbing of the nerves against the bony rims of the canals which are, in his opinion, responsible for the atrophy.

Acrocephaly and Mental Retardation

Most of the recorded cases of acrocephaly were either very young infants or mentally retarded children. It is difficult to assess the incidence of mental retardation in the group as a whole. According to Günther (1931) 20 per cent. of acrocephalic individuals in his series showed slight mental retardation, but this could be an underestimate for the pathological syndromes under discussion here since, as mentioned already, a single abnormality of one physical measurement was sufficient to place the individuals concerned in Günther's acrocephalic group. Similar considerations apply to the group of 37 African children showing "cranistenosis" with oxycephaly and scaphocephaly studied by Gordon (1959); none of his cases presented any neurological or mental abnormality.

There seems to be no doubt that a number of individuals exhibiting the whole, or a considerable part of any of the acrocephalic syndromes are mentally retarded and, sometimes, severely so. Five of Blank's (1959) 37 cases were, for example, patients in mental deficiency hospitals but examples were specially sought in such hospitals. Three of these were rated as feebleminded, one imbecile and one an idiot. However, some of the cases may be of average or even, albeit rarely, above average intelligence (Kahn and Fulmer, 1955). One of Blank's (1959) cases had an I.Q. of 120 (personal communication). He states, however, that some mental impairment was judged to be present in every one of his cases of Apert's syndrome (Blank, 1960). On the other hand, it is noteworthy that, in spite of many pronouncements in the literature as to the danger of developing mental deterioration in cases of acrocephaly with an initially normal intelligence, there is no published evidence that this is really so. On reading the very lengthy case reports, one is struck on the contrary by the non-progressive nature of the conditions described.

As could be foretold from the general rarity of the acrocephalic syndromes, affected individuals are also in a small minority among other mental defectives. Thus, in a series of some 2,000 admissions at the Fountain Hospital, only 11 were classified as acrocephalic and 14 as having hypertelorism. Most of these cases had only a minor degree of the deformity; one had full acrocephalosyndactyly.

Other Symptoms

Raised intracranial pressure has been also held responsible for other symptoms in acrocephaly: anosmia, headaches, paralysis and epilepsy. Other symptoms include ophthalmoplegia (Kreindler and Schachter, 1934), nystagmus and vestibular disturbance, while progressive middle ear deafness has been described by Heuyer, Lebovici and Homualk (1950) and attributed to ankylosis of the ossicles. It is difficult to estimate the frequency of these signs but they are certainly uncommon in typical cases. Thus the 3 cases of acrocephalosyndactyly recorded by Gross (1957) showed no "neurological" symptoms and disc changes, in spite of well marked "digital impressions" in the skull. Case 4 in his series, without syndactyly and complicated by cerebral hernia, presented, on the other hand, both epilepsy and paralysis.

It is necessary to restate the argument used already in relation to "optic atrophy": mentally defective individuals are often the victims of epilepsy and paralysis, but these are by no means always the result of high intracranial pressure and there is, in fact, no certain evidence linking such symptoms specifically with raised pressure in acrocephaly.

Surgical Treatment

All the procedures recommended for the relief of the cranio-dysostoses, i.e., in the main acrocephaly and scaphocephaly, aim at securing greater freedom for the expansion of the growing brain by artificially dividing the cranial bones and thus re-establishing, for a time, flexibility and elasticity in the already hardened skull (Bennett, Keegan and Hunt, 1936; King, 1938; Dandy, 1943; Mount, 1947; Ingraham, Alexander and Matson, 1948; McLaurin and Matson, 1952; Laitinen and Sulamaa, 1954–55; Mullan, 1960). The procedures include linear craniectomy, morcellation, subtemporal decompression, and cranioplasty and duraplasty. If valid, the claims for the success of such treatment could be interpreted as evidence in support of the theory of restriction of bone growth by "craniostenosis".

However, many of the reported cases appear to have shown no abnormality other than highheadedness or scaphocephaly, having no mental retardation or other cranial or skeletal features of acrocephalosyndactyly. The C.S.F. pressure has not been often recorded and, indeed, most authors have advocated and resorted to surgical intervention before the anticipated rise in intracranial pressure. In other cases, the operation appears to have been undertaken chiefly for cosmetic reasons. Neither descriptions nor photographs of the patients before and after treatment entirely convince the reader that similar or better general results could not have been had without operation.

Since mental or physical progressive deterioration is probably infrequent in the acrocephalic syndromes, some degree of progress can be expected simply from growing up, and it is therefore difficult to accept the claims made for surgery. Nevertheless, there is perhaps some reason to believe that the patient's appearance may be improved in certain selected cases (Mullan, 1960).

This is not to deny that raised intracranial pressure, amenable to surgical measures, may develop for incidental reasons in some acrocephalic individuals. It is, moreover, possible that cases of widespread cranial and cerebral deformity, such as acrocephaly, might be (Dussik, 1949) more than normally prone to such a complication, but this is still far from proven.

Pathological Data

It remains now to consider the recorded pathological findings. Unfortunately, save for some meticulously thorough descriptions of the cranial and skeletal changes, pathological data are exceedingly scanty. Thus, Eshbaugh (1948) found only 25 references to the state of the brain in the literature, and observed that in 15 of these the brain was merely described as normal. Even the weights of the brains were only recorded in a few cases, and these were within normal limits. The fullest summaries of the pathology are contained in the reports of Günther (1931), Valentin (1938), Gross (1957) and Blank (1959).

The shape of the brain conforms to the contours of the skull: it is abnormally high, shortened antero-posteriorly with the temporal lobes orientated more vertically than usually. Allowing for the general change in orientation, the pattern of gyri is usually normal, although some may be situated below the

level of the neighbouring convolutions. The meninges have been mostly normal except in the cases of Eshbaugh and Case 4 of Gross (1957), which showed localized thickening. Vascular abnormality has only been reported in the above-mentioned Case 4 of Gross, which also had unilateral stenosis of the jugular foramen and absence of the sigmoid sinus as well as cerebral herniation.

Flattening of the convolutions with pressure-coning of the brain-stem has been only described in Cases 4 and 5 of Gross (1957), although an early report by Wheaton (1894) referred to "bulging" of the brain when the dura was incised. Park and Powers (1920) mentioned "convolutional atrophy" without specifying this any further.

Ventricular dilatation, mild or moderate, has been mentioned by Eshbaugh (1948), Valantin (1938), Ripeing (1919) and by Martischnig and Thalhammer (1952) and Böök and Hesselvik (1953). Blank (1959) found 6 instances of ventricular dilatation in the literature, including some of those referred to already. The dilatation was recognized either radiologically or at post-mortem. Three of his own cases showed evidence of ventricular dilatation during life and four at autopsy. Hydrocephalus was also present in a case recorded by Jacobsen (1930). It is likely that, in this instance, ventricular dilatation was non-obstructive in origin since the skull was plagiocephalic and one of the cerebral hemispheres markedly atrophic. Compensatory ventricular dilatation following underdevelopment of the neighbouring neural tissue may also be the true explanation of the hydrocephalus in most of the other cases.

By contrast, Case 5 of Gross (1957), a girl aged 4 months, showed changes which could be more clearly attributed to raised intracranial pressure. The ventricles were considerably dilated, the convolutions were flattened and the corpus callosum and septum pellucidum had undergone atrophy. The white matter was thinned and showed moderate gliosis on histological examination. It is noteworthy, however, that in spite of these indications of raised intracranial pressure and the presence of marked digital impressions, the fundi were normal.

Other recorded pathological data include a single example, certainly incidental, of inflammatory meningeal and cerebral change. A few brains have shown evidence of gross cerebral dysplasia. The corpus callosum was absent in two cases: in one of Valentin's (Case 6) and in another of Swanzy (1898). The above case of Valentin showed also a marked polygyric deformity with enlargement of parts of both cerebral hemispheres. Hypoplasia of the corpus callosum was present in one of Gross' cases, and absence of the septum pellucidum, diagnosed only by radiology, in a case reported by Zellweger and Muralt (1952). Visceral changes had been wholly unspecific. In one of Valentin's (1938) cases all endocrine glands were examined, showing no histological abnormality. The association of the cranio-facial dysostosis with spina bifida, syringomyelia and hydrocephalus has been reviewed by Kissel, Dureux and Tridon (1959). They stress that the cranio-facial dysostoses are often associated with indubitable malformation of the eyes and central nervous sytem.

I am able to add to the above the following summary of a further case, which it is hoped to publish more fully elsewhere.

This girl, S. T. (Fig. 1), born with all the features of acrocephalosyndactyly, comes from a family free from other congenital disease. An X-ray report at 2 months stated that "most of the sutures of the vault appear to be fused except for the sagittal suture and the fontanelles. Posteriorly there is a moderate degree of craniolacunation. The anterior fossa is short and the middle fossa and sella lie almost in a vertical plane." She had a marked high palate. No clinical evidence of raised intracranial pressure was noted at any time. An operation

was performed at 4 months, strips of bone "including the coronal and lambdoid suture" being removed and tantalum foil inserted over the bone edges. It was recorded at operation that the two halves of the coronal suture were firmly fused and the suture itself presented as a small white ridge. The right half of the lambdoid suture was completely united, as was the lower half of the left one, but the upper half of the left one was described as still patent. The sagittal suture was widely open.

FIG. 1.—Patient, aged 14 months.

The patient's mental development was abnormally slow and at one year her mental level was assessed at 4 months on the Vineland Social Maturity Scale. Nevertheless, in the end she learned to walk and tried hard to talk, although her speech remained very indistinct. Optic atrophy did not develop. She had slight swelling of the nipples and enlargement of the clitoris. The patient succumbed rather suddenly to respiratory infection at 5 years.

At autopsy, the typically acrocephalic skull showed protruding fragments of tantalum foil on its surface, while most of the foil had been incorporated into the fully fused bones in the areas corresponding to the coronal and lambdoid sutures. Many lacunae became evident after macerating the skull. They were particularly conspicuous near or at the otherwise fully united bones at the

site of the operation. The interior of the skull showed the usual deformities associated with acrocephaly, notably, digital impressions and exaggerated relief markings (Fig. 2).

The brain was normal in weight (1,345 g.), its shape corresponding to the malformed cranium. As mentioned already, the gyri fitted closely into the grooves and lacunae of the skull. Allowing, however, for the anomalous form of the brain, the pattern of gyri appeared normal. There was no evidence of

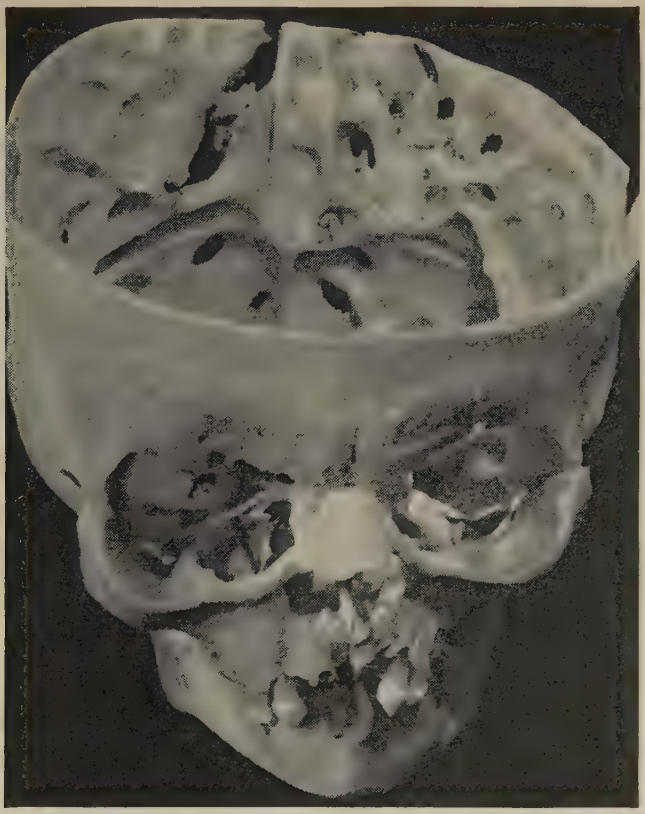


FIG. 2.—Oblique photograph of the skull to show exaggeration of relief markings and the perforations.

past or present rise in intracranial pressure either on naked-eye or histological examination. In appropriately-stained sections, the cerebral cortex showed some blurring of lamination and neuronal scarcity, most marked at the bottom of the sulci. Moderate neuronal deficiency was also present in the Sommer sector of the hippocampus. Glial cells and fibres were slightly increased around the 3rd and 4th ventricles. A small nodule of ectopic cortex was seen in the cerebellar white matter, and a few very small foci (200–300μ) of softening with microglial replacement were present in the descending root of the 5th nerve of the medulla and in the anterior column of the spinal cord. The optic nerves and tracts were normal.

All somatic organs were also examined, the only noteworthy changes being found in the salivary glands, which showed chronic non-specific inflammation, and in the lungs, which presented multifocal collapse and bronchiolar infection.

It may thus be concluded upon the available, rather unsatisfactory, pathological information that there has been either no evidence, or no certain evidence, of raised intracranial pressure in the great majority of cases. This is particularly significant since most of the pathological reports referred to infants and young children, and fatal cases, being usually the frailest and most handicapped of the group, may be expected to exhibit greater pathological changes than survivors.

Some of the equivocal changes such as ventricular dilatation can be more reasonably interpreted as evidence of congenital cerebral dysplasia, of which there were also other manifestations, such as absence of hypoplasia of the corpus callosum and septum pellucidum.

Conclusions

It would seem to follow from the above review that mechanical factors have been overstressed in considering the pathogenesis of acrocephaly. The theory formulated by Virchow (1852) rests upon untenable premises. Whilst present knowledge is still insufficient for the formulation of an alternative theory, certain facts may be significant.

There is, *firstly*, the association of the cranial with other evidence of skeletal and general dysplasia. This must mean that the area of embryonic dysosteogenesis can be either wide or narrow, and any explanation must account for both the general disturbance and localizing factors. These processes are associated, *secondly*, with cerebral dysplasia which may, in its turn, be either gross, as in the cases showing absence of the corpus callosum, or less obvious and even not apparent or entirely absent. *Thirdly*, the digital impressions of the skull are true imprints of the cerebral convolutions. The latter do not normally begin to assume their definitive shape till the seventh month of intrauterine life. Taken together with other evidence of much earlier dysosteogenesis, viz., failure of separation of the digital bones in the limb buds and anomalies in the situation of the centres of ossification in the cranial bones, the evidence indicates no finite event but a lasting process. This is further supported by the curious phalangeal outgrowths in older individuals. *Fourthly*, since, as seems likely, the cranial impressions are not the result of raised intracranial pressure, the appearances point to an altered responsiveness of the bones to normal pressure, traction or other inductive factors in contiguous structures, including other bones. That this is so is even clearer from the exaggerated relief markings on the inner surface of the skull, the failure of separation of the cranial and digital bones, and the occasional changes in some of the joints.

As a hypothesis, it may be permissible to translate these circumstances into terms of possible biochemical events by postulating a disturbance in the nature and/or synergistic action of interdependent enzymes and possibly other biochemical factors concerned chiefly in osteogenesis. This disturbance may reach out, temporally or spatially, to neighbouring systems such as those involved in cerebral morphogenesis. The underlying biochemical abnormality, which may be genetic in origin, begins to manifest itself in early embryonic life producing the maximum amount of deformity at the time of the greatest growth and differentiation and thereafter becoming less apparent. Nevertheless, the facts suggesting that the underlying disturbance persists, if only in a modified or latent form, hold out the promise of a profitable biochemical search in patients of every age.

References

APERT, M. E., "De l'acrocéphalosyndactylie", *Bull. Soc. méd. Hôp., Paris*, 1906, **23,** 1310.
Idem and REGNAULT, F., "La dysostose acrocéphalique (à propos de l'étude du crâne d'un acrocéphalosyndactyle)", *Bull. Soc. méd. Hôp., Paris*, 1929, 832.
ATKINSON, F. R. B., "Hereditary cranio-facial dysostosis, or Crouzon's disease", *Med. Press*, 1937, **195,** 118.
BENDA, C. E., *Developmental Disorders of Mentation and Cerebral Palsies*, 1952, New York: Grune & Stratton, p. 147,
BENNETT, A. E., KEEGAN, J. J. and HUNT, H. B., "Oxycephalus: premature synostosis of the cranial sutures", *J. nerv. ment. Dis.*, 1936, **84,** 274.
BLANK, C. E., *The Genetics of Acrocephalosyndactyly*, 1959, Thesis. London University.
Idem, "Apert's syndrome (a type of acrocephalosyndactyly)—observation on a British series of thirty-nine cases", *Ann. Hum. Genet., Lond.*, 1960, **24,** 151.
BOLK, L., "On the premature obliteration of sutures in the human skull", *Amer. J. Anat.*, 1914–15, **17,** 495.
BÖÖK, J. A., and HESSELVIK, L., "Acrocephalosyndactyly", *Acta. paediat.* (*Uppsala*), 1953, **42,** 359.
BRONFENBRENNER, A. N., "A case of skull deformity related to the so-called acrocephalosyndactylia", *Psychiat. Quart.*, 1932, **6,** 612.
BUCKLEY, R. W., and YAKOVLEV, P. I., "Dysostosis of skull, face and extremities (acrocephalosyndactyly)", *Amer. J. Dis. Child.*, 1948, **75,** 688.
BUSSOLA, E., "Acrocefalosindactilia e atrofia postneuritica dei nervi ottici", *Riv. oto-neuro-oftal.*, 1928, **5,** 503.
COHN, B. N. E., "True oxycephaly with syndactylism. Case report", *Amer. J. Surg.*, 1945, **68,** 93.
CANDREVIOTIS, N., "Zur Entstehung des Lückenschädels", *Frankfurt. Z. Path.*, 1955, **66,** 449.
CARPENTER, G., "Two sisters showing malformation of the skull and other congenital abnormalities", *Reports of the Society for the Study of Diseases in Children*, 1901, **1,** 110
CHOTZEN, F., "Eine eigenartige familiale Entwicklungsstörung (Akrocephalosyndaktylie, Dysostosis craniofacialis und Hypertelorismus)", *Mschr. Kinderheilk.*, 1932–33, **55,** 97.
CLARK, W. E. le G., *The Tissues of the Body*, 2nd ed., 1945, Oxford: Clarendon Press, p. 87.
CROME, L., "The brain and mental retardation", *Brit. méd. J.*, 1960, *i,* 897.
CROUZON, O., "Dysostose cranio-faciale héréditaire", *Bull Soc. méd. Hôp., Paris*, 1912, **33,** 545.
Idem, Études sur les Maladies Familiales Nerveuses et Dystrophiques, 1929, Paris: Masson, p. 278.
DANDY, W. E., "An operation for scaphocephaly", *Arch. Surg.* (*Chicago*), 1943, **47,** 247.
DAVIS, B. F., "Acrocephalosyndactylism", *Amer. J. Dis. Child.*, 1915, **9,** 446.
DAVIS, F. A., "Tower skull, oxycephalus", *Amer. J. Ophthal.*, 1925, **8,** 513.
DORFMANN, R., "Über Pathogenese und Therapie des Turmschädels", *v. Graefes Arch. Ophthal.*, 1908, **68,** 412.
DUSSIK. K. T., *Zentralnervensystem und Sauerstoffmangelbelastung.*, 1949, Wilhelm Maudrich, Vienna.
ESHBAUGH, D., "Relation of the changes in the brain to those in the skull of Crouzon's and similar diseases; with report of a case", *J. Neuropath.*, 1948, **7,** 328.
FERRIMAN, D., *Acrocephaly and Acrocephalosyndactyly.*, 1941, London: Oxford University Press.
FLETCHER, H. M., "On oxycephaly", *Quart. J. Med.*, 1910–11, **4,** 385.
FRANCESCHETTI, A., and KLEIN, D., "The mandibulo-facial dysostosis. A new hereditary syndrome", *Acta ophthal.* (*kbh.*), 1949, **27,** 141.
GRAINGER, R. B., O'DELL, B. L., and HOGAN, A. G., "Congenital malformations as related to deficiencies of riboflavin and vitamin B_{12}, source of protein, calcium to phosphorus ratio and skeletal phosphorus metabolism", *J. Nutr.*, 1954, **54,** 33.
GREIG, D. M., "A hitherto undifferentiated congenital cranio-facial deformity", *Edinb. med. J.*, n.s., 1924, **31,** 560.
Idem, "Oxycephaly", *ibid*, n.s., 1926, **33,** 189, 280 and 357.
Idem, "Acrodysplasia. Type: syndactylic oxycephaly", *ibid*, n.s. 1935, **42,** 537.
GREWEL, F., "Untersuchung ueber Hypsicephalie, Turricephalie und praemature Synostose der Suturae coronariae", *Acta neerl. Morph.*, 1948–49, **6,** 145.
GROSS, H., "Zur Kenntnis der Beziehungen zwischen Gehirn und Schädelkapsel bei den Turricephalen, craniostenotischen Dysostosen", *Virchows Arch. path. Anat.*, 1957, **330,** 365.
GÜNTHER, H., "Der Turmschädel als Konstitutionsanomalie und als klinisches Symptom", *Ergbn. inn. Med. Kinderheilk.*, 1931, **40,** 40.
Idem, "Dysostosis craniofacialis hereditaria", *Endokrinologie*, 1933–34, **13,** 255.
Idem, "Hypertelorismus", *Ibid.*, 1933–34, **13,** 61.
HEUYER, G., LEBOVICI, S., and HOMUALK, J., "Un cas de maladie de Crouzon avec surdité progressive. Encéphalographie gazeuse", *Arch. franç. Pediat.*, 1950, **7,** 278.
HÖVELS, O., "Zur Systematik der Missbildungen des I. Visceralbogens unter besonderer Berücksichtigung der Dysostosis mandibulo-facialis", *Z. Kinderheilk.*, 1953, **73,** 532 and 568.
HOWKINS, J., JEFFERISS, D., and HANDLEY, R. S., "True Oxycephaly", *Lancet*, 1938, *ii,* 1226.

INGRAHAM, F. D., ALEXANDER, E., and MATSON, D. D., "Clinical studies in craniosynostosis", *Surgery*, 1948, **24,** 518.
JACOBSEN, A. W., "Premature synostosis of cranial sutures. A report of five cases", *Arch. Pediat.*, 1930, **47,** 556.
JAENSCH, P. A., "Schädeldysostosen", *Z. ges. inn. Med.*, 1952, **7,** 426.
JENSCH, N., "Zur Genealogie und Klinik des Turmschädels", *Arch. Psychiat. Nervenkr.*, 1941–42, **114,** 444.
KAHN, A., and FULMER, J., "Acrocephalosyndactylism", *New Engl. J. Med.*, 1955, **252,** 379.
KING, J. E. J., "Oxycephaly. A new operation and its results", *Arch. Neurol. Psychiat. (Chicago)*, 1938, **40,** 1205.
KISSEL, P., DUREUX, J.-B., and TRIDON, P., "Incidence des malformations du système nerveux au cours de malformations du squelette cranio-facial", p. 159, 1959, In *Malformations Congénitales du Cerveau*, ed. by Heiyer, Feld and Gruner. Paris: Masson.
KREINDLER, A., and SCHACHTER, M., "Sur une forme particulière de malformation cranio-faciale (acrocéphalo-syndactylie, asymétrie faciale et ophtalmoplégie)", *Paris med.*, 1934, *ii*, 102.
LAITINEN, L., *Craniosynostosis. Premature Fusion of the Cranial Sutures*, Helsinki, *Ann. Paediat. Fenn.*, 1956, **2,** suppt. 6.
Idem, and SULAMAA, M., "Craniosynostosis. Symptoms and results of treatment", *Ann. Paediat. Fenn.*, 1954–55, **1,** 283.
MCLAURIN, R. L., and MATSON, D. D., "Importance of Early Surgical Treatment of Craniosynostotis", *Pediatrics*, 1952, **10,** 637.
MARTISCHNIG, E., and THALHAMMER, O., "Acrocephalosyndaktylie. (Erörterung der Genese vom Gesichtspunkt der Embryopathie)", *Helv. paediat. Acta*, 1952, **7,** 257.
MOUNT, L. A., "Premature closure of sutures of cranial vault—a plea for early recognition and early operation", *N. Y. St. J. Med.*, 1947, **47,** 270.
MULLAN, S., "Late moulding of scaphocephalic skull", *J. Dis. Child.*, 1960, **99,** 55.
PARK, E. A., and POWERS, G. F., "Acrocephaly and scaphocephaly with symmetrically distributed malformations of the extremities", *Amer. J. Dis. Child.*, 1920, **20,** 235.
RATHER, L. J. (Trans.), *Virchow, R. Disease, Life and Man.*, p. 13, 1958. Stanford: Stanford University Press.
RIEPING, A., "Zur Pathogenese des Turmschädels", *Dtsch. Z. Chir.*, 1919, **148,** 1.
RUH, H. O., "Acrocephalosyndactylism—a teratological type", *Amer. J. Dis. Child.*, 1916, **11,** 281.
SCHÖNENBERG, H., "Schädeldysostosen", *Ärztl. Wschr.*, 1958, **13,** 909.
SHERNE, J., "Dislocation of the eyeball as a complication of oxycephaly", *Brit. med. J.*, 1938, *i*, 565.
SIRKIN, J., "Acrocephalosyndactylia: report of a case", *Amer. J. ment. Defic.*, 1943–44, **48,** 335.
STEWART, R. M., "The nervous system in cleidocranial dysostosis: report of a case", *J. Neurol. Psychopath.*, 1928–29, **9,** 217.
SWANZY, H. R., "On some of the congenital anomalies of the eye", *Trans. ophthal. Soc. U.K.*, 1898, **18,** 1.
THOMA, R., "Über die prämaturen Synostosen der Schädelnähte und über das Wachstum, die Seneszenz und die Hyperostose des Schädels.", *Beitr. path. Anat.*, 1923–24, **72,** 207.
UHTHOFF, W., "Über hochgradigen Exophthalmus bei Schädeldeformität", *Klin. Mbl. Augenheilk.*, 1905, **43,** 1.
VALENTIN, B., "Die Korrelation (Koppelung) von Missbildungen, erläutert am Beispiel der Akrocephalosyndaktylie", *Acta orthop. scand.*, 1938, **9,** 235.
VIRCHOW, R., "Ueber den Cretinismus, namentlich in Franken, und über pathologische Schädelformen", *Verh. phys.-med. Ges., Würzburg*, 1852, **2,** 230.
WEECH, A. A., "Combined acrocephaly and syndactylism occurring in mother and daughter. A case report", *Bull. Johns Hopk. Hosp.*, 1927, **40,** 73.
WEYGANDT, DR., "Der Geisteszustand bei Turmschädel", *Dtsch. Z. Nervenheilk.*, 1921, **68** and **69,** 495.
WEYERS, H., "Zur Klinik und Pathologie der Dysostosis mandibulo-facialis", *Z. Kinderheilk.*, 1915, **69,** 207.
WIGERT, V., "Die Akrozephalosyndaktylie. Weiteres über die allgemeinen Skelettveränderungen", *Acta psychiat. (Kbh.)*, 1932, **7,** 701.
WHEATON, S. W., "Two specimens of congenital cranial deformity in infants associated with fusion of the fingers and toes", *Trans. path. Soc. Lond.*, 1894, **45,** 238.
ZELLWEGER, H., and VON MURALT, G., "Zur Pathologie des Septum pellucidum im Pneumoencephalogramm (PEG)", *Helv. paediat. Acta*, 1952, **7,** 229.
ZUNIN, C., "L'ipertelorismo di Greig e suoi rapporti con le sindromi di disostosi craniche e facciali", *Minerva pediat. (Torino)*, 1955, **7,** 71.

TREATMENT OF MONGOLISM WITH PITUITARY EXTRACT

By

J. M. BERG, M.B., B.Ch., M.Sc.

B. H. KIRMAN, M.D., D.P.M.

J. STERN, Ph.D.

Fountain Hospital, London

and

URSULA MITTWOCH, Ph.D.*

Galton Laboratory, University College, London

WHEN mongolism was first described, it was considered by some authors to be a form of cretinism (Seguin, 1866), and with the discovery of the effect of thyroid treatment in cretinism, this was tried in mongolism also. The disappointing results diverted attention to other endocrines. Tredgold, in 1929, was recommending a mixture of thyroid, pituitary, thymus, suprarenal and pineal glands, though he did not believe that such treatment was curative.

Many observers have considered that there is a disturbance of pituitary function in mongolism and some that pituitary therapy is beneficial. In particular Benda (1947), stated that "mongolism is the congenital type of hypopituitarism". His views, however, largely depend on his own somewhat unorthodox interpretation of the histological findings in the pituitary in mongolism. In reference to 100 children treated with a small dose of thyroid and a calf pituitary powder (Armour) given orally, Benda (1953) claimed that "it is possible nowadays to influence the physical growth of the mongoloid child to such an extent that he remains within the average range of height and weight" and that, in regard to mental development, "some of the children made amazing progress". After 10 years' experience of this form of treatment, Benda (1956) observed that some children "lose their 'mongoloid' appearance almost completely" and that the influence on mental development is "less striking but appears definite" if many untreated children are compared with his group of over 100 treated cases. Carter (1958), in a preliminary report on the use of an oral preparation of young calf pituitary extract in mongolism, also claimed some excellent results both in terms of physical and mental development. Blumberg (1959), using an oral preparation of pituitary extract, in this case from adult animals, plus thyroid, claimed good physical development in 11 cases of mongolism during the 2-year treatment period. An influence on mental growth could not, however, be established.

Some of these claims are unconvincing because of inadequate data on methods for selection of patients, criteria for assessing progress and/or absence

* External Scientific Staff, Medical Research Council.

of controls. Nevertheless, they arouse considerable interest among parents of children with mongolism who may feel that, if their children are not given what is asserted to be effective treatment, an opportunity is being missed. It was therefore decided to attempt to assess the value, if any, of pituitary administration.

Since there is uncertainty about the effectiveness of *oral* preparations of pituitary, as they may be destroyed by the gastric juices (Benda, 1956; Carter, 1958), we tried to obtain for our trial an active preparation which could be given by injection. Through the courtesy of Dr. F. Paulsen, a quantity of "Somacton" (Ferring AB) sufficient to treat 3 children daily for 6 months was made available to us. "Somacton" is a growth hormone preparation extracted from hog pituitary glands as a by-product of A.C.T.H. production. The makers state that it is certain that this preparation is active in humans and differs from other preparations in that it is more soluble, purer, and free from A.C.T.H. contamination.

Method

Three pairs of mongols, all in-patients in the Fountain Hospital, were matched as closely as possible for age, sex, weight, height and mental level. The youngest patients available were chosen, since it has been suggested by Benda and others that such children derive most benefit from pituitary therapy. All six children appeared free from intercurrent illness when selected for the trial and none had specific motor defects. All were transferred to the same small ward prior to commencement of the trial and remained there throughout, thus ensuring as constant an environment and diet as possible.

Before the trial, intelligence tests were carried out; weights, heights and head circumferences recorded; serum calcium and phosphate values determined; neutrophil lobe, neutrophil and lymphocyte counts done; and skull radiography and electro-encephalography undertaken. All the investigations were repeated at the end of the trial and the leucocyte studies also during it.

One of each of the 3 pairs of mongols, chosen at random, was given 100 tibia units of "Somacton" subcutaneously, daily (this dose corresponding to 2 international units), the other having a like amount of a control injection consisting of 0·5 ml. normal saline. Daily pituitary extract and control injections were given for a period of 6 months from August, 1958 to February, 1959. There were 2 breaks of 6 and 8 days due to delayed arrival of supplies. Also, the special pituitary preparation in the form of ampoules containing 5 mg. of lyophilized powder ("Somacton") was replaced during the last month of the trial, because of termination of supplies, by the ordinary commercial preparation of "Somacton" containing 500 tibia units per ampoule; the same dose was, however, maintained. Throughout the trial, the powder was made up freshly daily with 0·5 ml. of solvent for each child. The key to the identity of the injections was kept by the Chief Pharmacist and none of the observers taking part in the trial was informed which child was having which injection.

Results

The results of mental, physical and biochemical measurements are shown in Table I and of leucocyte counts in Table II. In these tables, 1, 2 and 3 indicate the three matched pairs of mongols, A those who received pituitary extract injections and B those who received placebo injections.

TABLE I

Mental, Physical and Biochemical Measurements Before and After Trial

Case	Sex	Before							After						
		Age	I.Q.	Weight	Height	Head Circum-ference	Serum Calcium	Serum Phos-phate	Age	I.Q.	Weight	Height	Head Circum-ference	Serum Calcium	Serum Phos-phate
1 A ..	F	16	54	7·77	72·0	41·2	8·9	4·9	22	44	9·68	74·5	42·2	8·8	4·5
1 B ..	F	16	48	7·03	69·5	42·3	8·9	4·8	22	31	8·45	72·0	43·0	8·9	5·0
2 A ..	M	25	23	7·51	73·5	44·8	9·2	4·6	31	16	8·90	75·5	45·3	8·2	4·4
2 B ..	M	27	32	11·28	80·0	47·0	9·5	5·2	33	30	13·47	82·5	47·6	9·2	4·5
3 A ..	M	48	40	15·54	93·5	46·5	9·2	4·5	54	38	16·53	94·5	46·7	8·8	4·5
3 B ..	M	48	30	13·83	87·5	47·5	8·9	4·4	54	31	14·26	89·0	47·7	9·4	4·3

I.Q. assessed on Griffiths Mental Development Scale.

Age expressed in months, weight in kg., linear measurements in cm., and serum calcium and phosphate levels in mg. per 100 ml.

TABLE II

Neutrophil Lobe, Neutrophil and Lymphocyte Counts Before, During and After Trial

Counts	Case	Before Trial	During Trial	After Trial	Difference During–Before Trial	t	P
Mean neutrophil lobe counts	1 A	1·41	1·57	1·61	0·16	2·640	0·060
	2 A	1·32	1·59	1·52	0·27		
	3 A	1·54	1·67	1·51	0·13		
	1 B	1·80	1·83	1·62	0·03		
	2 B	1·63	1·60	1·70	−0·03		
Average neutrophil counts	1 A	4,780	7,990	5,126	1,496	2·927	0·044
	2 A	3,433	7,369	5,349	3,210		
	3 A	3,578	5,074	4,256	3,936		
	1 B	5,763	4,903	5,071	−860		
	2 B	2,795	2,394	4,133	−401		
Average lymphocyte counts	1 A	4,546	3,228	4,739	937	0·223	0·85
	2 A	1,943	2,873	3,692	−1,318		
	3 A	2,325	3,262	2,233	930		
	1 B	2,693	5,455	3,163	2,762		
	2 B	1,234	2,104	1,607	1,607		

Each entry in the columns headed before, during and after trial represents the average of 3 determinations.

No differences between the two groups before and after the course of injections were apparent in terms of mental development and physical measurements (Table I). Likewise, X-ray examination of the skulls and electroencephalograms revealed no changes which could be attributed to the pituitary extract. Clinically, observation of the children by medical and nursing staff throughout and after the trial produced no evidence of differences between the two groups. In children with mongolism the serum calcium tends to be low and the serum inorganic phosphate slightly raised (Stern and Lewis, 1958). There was no indication in this trial that the pituitary injections tended to raise the serum calcium or lower the serum phosphate levels (Table I).

The leucocytes in mongolism show two peculiarities: (*a*) a reduction in the average number of lobes of the neutrophils and (*b*) a higher neutrophil count and lower lymphocyte count than in other children of the same age group (Mittwoch, 1958). In view of this, mean lobe counts of the neutrophils and total neutrophil and lymphocyte counts were done on the patients taking part in the trial on 3 occasions before, 3 occasions during and 3 occasions after the course of injections, so as to see whether these variables were affected by the treatment. Counts were performed without knowledge of the origin of the slides. One of the patients (Case 3B) developed glandular fever (?) before injections commenced, with a lymphocyte count of 32,000 per c.mm. and a neutrophil count of 11,000 per c.mm. As a count of this magnitude would have swamped all comparisons, this patient was excluded for the purpose of evaluating leucocyte counts. Since he received the placebo, the present results are based on 3 patients receiving the pituitary extract and 2 controls (Table II). With regard to the mean neutrophil lobe counts, there was a slight increase during treatment in the 3 patients receiving pituitary injections and no increase

in the 2 patients receiving placebo injections. However, the mean lobe counts of the latter patients was altogether higher than those of the former ones. With regard to the neutrophil counts, the 3 patients receiving pituitary injections showed an increase in neutrophils during treatment and a fall thereafter; no such effect occurred in the 2 patients on placebo injections. As for the lymphocyte counts, there were no consistent changes in either group. Bearing in mind the extreme caution required in interpreting results based on 3 cases, the present data suggest that the pituitary extract produced an increase in the neutrophil counts. As there was no increase in lymphocyte counts, the ratio of neutrophils to lymphocytes, which in any case tends to be elevated in children with mongolism, became even higher in the patients having pituitary injections.

Discussion

It is now generally considered that there is a considerable degree of species specificity in growth hormone preparations. Wilhelmi (1955) and Knobil (1955) failed to demonstrate any consistent effect of bovine hormone in monkeys, and suggested that the ineffectiveness of this preparation in man and monkey was due to species difference in hormone composition. Raben (1959) has reviewed the subject and concludes that "the available bovine and porcine growth hormones are not suitable for clinical use. There is also reasonable doubt that the anabolic effects seen in man were more than artefactual. Alternatively, it is necessary to believe that these preparations are only erratically and sporadically active in man."

Critical as we are of the claims made for pituitary therapy in mongolism in other reports, we are also conscious of the limitations of the present trial. We were unable to check independently the activity of our preparation in humans. Further, it could be argued that our conclusions would be more tenable if based on a larger and younger series and a longer trial. For practical reasons, this was not possible. Despite these limitations, however, we thought it worth recording this study since it adds to the weight of evidence which now suggests that, even when given by injection, bovine and porcine extracts are virtually ineffective in humans and consequently of no value in the treatment of mongolism.

There is now adequate evidence that human and monkey pituitary growth hormones are active in man (Beck, 1959; Beck *et al.*, 1957 and 1958). Though there is no *a priori* reason to suppose that an effective pituitary growth hormone will remedy the developmental abnormality in mongolism, it would seem worth while to try the human and monkey hormones in this condition in the hope of producing some amelioration. If such treatment is to be beneficial, it would probably be necessary to give it to very young infants, but a preliminary trial might be made on older patients to assess the effect on metabolism.

Summary

One of each of three matched pairs of mongols, aged 16 to 48 months, was given 100 tibia units of "Somacton" (a growth hormone preparation extracted from hog pituitary glands) subcutaneously, daily, for 6 months, the other receiving a daily control injection of 0·5 ml. normal saline. No significant differences were noted between the 2 groups after the trial in terms of intelligence, weight, height, head circumference and serum calcium and phosphate levels. Nor were there apparent differences in appearance, behaviour, skull X-ray and electroencephalographic findings. Those receiving pituitary

extract showed, during treatment, an increase in neutrophil counts; these changes did not occur in those receiving placebo. There was no consistent change in lymphocyte counts in either group.

This small study lends support to the view that porcine and similar pituitary growth hormones are of no value in mongolism. It is suggested that human and monkey preparations should be tried.

Acknowledgments

Our thanks are due to Professor L. S. Penrose and Dr. J. H. Ottaway for help and advice, to Dr. F. Paulsen and Messrs. Ferring AB of Malmö, Sweden, for supplying the "Somacton", to Dr. R. L. Quilliam for skull X-ray reports, to Dr. J. Foley for EEG reports, to Dr. Mary Woodward and Miss D. Slomson for psychological assessments, to Mr. W. H. P. Lewis for assistance with the biochemical investigations, and to Sister B. Whittle and the staff of the research unit at the Fountain Hospital for their co-operation.

References

Beck, J. C., *Proc. Roy. Soc. Med.*, 1959, **52,** 1047.
Idem, McGarry, E. E., Dyrenfurth, I., and Venning, E. H., *Science*, 1957, **125,** 884.
Iidem, *Ann. int. Med.*, 1958, **49,** 1090.
Benda, C. E., *Mongolism and Cretinism*, 1947. London, p. 138.
Idem, *Quart. Rev. Pediat.*, 1953, **8,** 79.
Idem, *Arch. Pediat.*, 1956, **73,** 391.
Blumberg, E., *J. Maine med. Ass.*, 1959, **50,** 120.
Carter, C. H., *J. Flor. med. Ass.*, 1958, **44,** 709.
Knobil, E., in: *The Hypophyseal Growth Hormone: Nature and Actions* (Smith, R. W., Gaebler, O. H., and Long, C. W. H.), 1955. New York, p. 255.
Mittwoch, U., *J. ment. Defic. Res.*, 1958, **2,** 75.
Raben, M. S., in: *Recent Progress in Hormone Research*, 1959, **15,** 71. New York and London.
Seguin, E., *Idiocy*, 1866. New York, p. 381.
Stern, J., and Lewis, W. H. P., *J. Ment. Sci.*, 1958, **104,** 880.
Tredgold, A. F., *Mental Deficiency*, 1929. London, p. 226.
Wilhelmi, A. E., in: *The Hypophyseal Growth Hormone: Nature and Actions* (Smith, R. W., Gaebler, O. H., and Long, C. W. H.), 1955. New York, p. 59.

AN ENQUIRY INTO THE REASONS FOR ADMISSION OF UNDER FIVE YEAR OLDS TO A MENTAL SUBNORMALITY HOSPITAL

By

V. L. KAHAN, L.M.S.S.A., D.P.M.

Consulting Psychiatrist
Pewsey Hospital
Consulting Children's Psychiatrist
Pewsey Hospital Group

THE value of medical and social services in the domiciliary care of the mentally subnormal child has been under considerable discussion during recent years. The mentally subnormal child is known to show many of the same traits as the normal child when removed from the type of personal relationship between mother and child, which is normal within the ordinary home. It is generally agreed that hospitalization of the normal child under five should be avoided if possible, but it must be remembered that this attitude is equally important in the case of the mentally abnormal or psychotic child. Indeed such children have great difficulty in coming to terms with their environment, and as a result are even more vulnerable to the breakdown of the mother/child relationship than the normal child. It is important, therefore, to look critically at the reasons given for applying for admission to a hospital for mental subnormality, and this study attempts to analyse the reasons put forward in a sample of patients admitted during the years 1955–59, and to discuss possible methods of improving the existing mechanisms.

Pewsey Hospital, with its ancillary unit, West Stowell House, for psychotic children, is in the Oxford Regional Hospital Board area. It takes patients from Berkshire, Buckinghamshire, Northamptonshire, Oxfordshire, Wiltshire and the County Boroughs of Oxford, Northampton and Reading. The area thus stretches from Metroland in Buckinghamshire on the outskirts of London to deep rural north-west Oxfordshire and Wiltshire. It includes a new town, Corby, and high-employment areas, with relatively large immigrant populations, such as Oxford and Swindon. Although it is primarily concerned with the Pewsey Hospital area, it shares the responsibility for the in-patient management of the mentally subnormal for the whole region, in conjunction with one other hospital.

In addition to the varied geographical conditions and social elements in the catchment area of the patients admitted to Pewsey Hospital and West Stowell House, it was soon evident from a preliminary reading of the referral notes that the expressed standards of need for admission varied greatly in the minds of the referring, certifying and recommending agents within the local authorities.

An important reason for limiting the survey to patients under five years of age was that these patients are sufficiently young not to present gross physical problems for parents, from the point of view of their physical weight and energy,

and being below five years of age the statutory requirements of education would not complicate an already complicated picture.

METHOD

This is a pilot investigation of approximately 30 per cent. of all the cases admitted, based on the scrutiny of the referral documents, from both medical and social agencies. Letters and reports from Medical Officers, Specialists, General Practitioners and Mental Health Workers of local authorities were studied, and are the source of the information which will be discussed.

This enquiry has been based solely on the information given by the referring agents in support of their applications.

For the purpose of the enquiry, need for hospitalization was assessed under various headings within both medical or social fields. The medical reasons for admissions were sub-divided into either primarily "for physical care and management", or "for mental treatment". The social elements were more detailed and came under the headings of family reasons, housing reasons and behavioural reasons.

The family reasons were divided into need for hospitalization on account of parental guilt feelings and rejection of the patient, and parental personal emotional instability, making either one or both parents unsuitable to manage their child.

Housing aspects are sub-divided into pressure from other children within the home, making the care of the patient difficult, or leading to neglect of the healthy children, there being too little space inside the house for the patient and the other children, or there being too little space outside the house for the patient's exercise and management. This latter would rarely apply, inasmuch as a large proportion of the children concerned would not be fully mobile. An additional element considered was the pressure of hostile neighbours on a family having a severely subnormal child, with the social complications to which this might lead. The factor of additional handicaps that arise from organic causes was looked for, for example, epilepsy, blindness, spasticity, gross hydrocephaly and so on. The availability of, and degree of, the use made of older children, relatives, etc., was also investigated to see how far such assistance affected the situation regarding the child's need to come into hospital. Also reports of efforts made by outside agencies to help the patient's family were looked for. These included statutory ones, medical and social, under the control of the local authority, and national voluntary ones interested in handicapped and deprived children.

In the survey, a further subdivision has been made into urban and rural communities.

The 21 cases in this pilot scheme are a random sample out of a total of 70 children under five, who were admitted to Pewsey Hospital for long-term care over the last five years, i.e. 1955–59. Nine were admitted for medical reasons and 12 for social ones: and 16 cases were from urban and only 5 from rural areas. Of the 9 cases referred for medical reasons, 8 came in primarily for physical care and only 1 for treatment. Guilt or rejection, or a combination of both, occurred in at least 8 of the 21 cases. This was directly expressed or appeared between the lines of the referral notes. It may well have been a fact in others, as it was not felt that the referring agent was necessarily aware of this complication, since there was infrequent mention of its possibility. Pressure of housing appeared, in the sense of there being too little space within the house

adequately to deal with the needs of the patient and the other children, but it was relatively uncommon, and was a major element in only 5 of the 21 referrals. On the other hand the feeling that the patient was giving rise to deleterious effects on the other children occurred in 9 cases and possibly in 2 more. Hostile neighbours making life more difficult for the parents of the handicapped child seems to have occurred only in one possible case. The "nuisance" side, it was interesting to note, was put forward in 19 of the 21 cases referred. Two of the 21 children referred had additional motor handicaps that led to a request for hospitalization. Blindness occurred in 5 cases and 3 out of 5 epileptics were severe cases.

TABLE

Reason for Referral	Urban	Rural	Total
Medical Care:			
Treatment	1		1
Nursing	1 1 1 1 1 1 1	1	8
Training			
			9
Social Care:			
Rejection by parents	1 1	1 1	4
Instability of parents	1 1		2
Pressure on other children	1	1	2
Toilet difficulties / Feeding difficulties	1 1	1	3
Danger to patient	1		1
			12

Study of the referral notes of the 21 children reveals that voluntary and statutory agencies are not mentioned in any of them as having been called upon to help. Thus the receiving agents at the hospital had little basis on which to assess the severity of the need for the child's admission against a background of previous efforts made on the child's behalf.

Nearly all the children under discussion showed regression as a result of their being admitted to hospital. This regression continued for greater or lesser periods, and many of them after many months continue to show effects of what is suspected as being deprivational symptoms, in addition to their mental subnormality or psychotic symptomatology.

This commonly demonstrated itself by children previously in some emotional contact at home becoming indifferent to the nursing staff and their attempts to comfort them, the loss of even partial capabilities in the areas of self help, such as feeding, toilet habits, sitting up, or being interested in locomotion. An increase of emotional lability with mood swings from seemingly meaningless laughter to crying for no externally visible reason, not settling for many months, has been noticed. Rocking, face slapping, head banging, rhythmic and athetotic movements, were further signs of emotional disturbance, giving rise to the release of anxiety behaviour. These phenomena to a large extent subside after varying lengths of time. This happens in a manner that suggests that the patient has eventually come to terms with his new environment, but at an effective level often still below that before admission.

It was thought that perhaps in isolated rural communities, where social services of various sorts would be less readily available, there might be a higher

rate of referral to hospitals, and that in urban areas, where community services are usually more readily available, there would be a diminution of hospitalization. In view of this, the rural community was regarded as one where the isolation was sufficient to limit the possibility of neighbour help.

Discussion

This pilot enquiry suggests that the grounds for referral and requests for admission, especially for children, to psychiatric hospitals, needs to be expert, inasmuch as this is one of the few branches of the hospital service in which priority of admission is largely in the hands of those who have little knowledge of the illnesses they are assessing or conditions inside the hospitals. Another important aspect, particularly in children, and more particularly with children under 5, is that the removal from the intimate inter-personal atmosphere of home to a larger institution where the amount of child/adult contact is necessarily limited, frequently leads to regression and withdrawal. As a consequence young children tend to become more retarded, and have to regain ground at a later stage, which would not have been lost had they been kept at home until they were older. The need for a close intimate relationship with a mother figure is as great, and in some ways greater, in the retarded child, even when grossly brain damaged, than in more normal ones. The views of Bowlby and others on the normal child's emotional needs are confirmed by the writer's observation of children who come under his care on account of their retarded, psychotic or severely disturbed emotional states.

Conclusions

There would appear to be good grounds for closer liaison between the hospitals and the agencies which come into contact with children in their homes. Those in the hospital feel acutely absence of information, and are often under a handicap in dealing with patients' admission.

1. The present method of referring children, under 5 years of age, to the hospital appears unsatisfactory. Criteria for admission seem variable in quality and less informative than is desirable.

2. Referring notes do not give an impression that referring agents are fully aware of the seriousness of the step of removing very young infants from their mothers, or mother substitutes.

3. There are major differences in the quality of the reports between individuals and areas.

4. In spite of the benefits to all concerned, the patient, the family, the bed state of the hospitals, and the national exchequer, domiciliary services do not appear to have been used to help parents look after their handicapped children at home.

5. Parent exhaustion and exasperation is a major factor in requests for hospitalization. A detailed enquiry, assessing the real need for infant beds in hospitals for the severely retarded or psychically ill child is not possible using the material available for this enquiry, inasmuch as there were no records of what may have been done to help the parents look after their child at home.

6. A detailed investigation by trained social workers, under a unified scheme, would be required to study how far, using the available social and medical supportive methods, parents can be helped to keep their young children

at home, and what may be lacking under present circumstances to bring this about.

7. The multiplicity of local authorities with varying standards of non-professional staffs referring cases makes objective assessment of claims for hospitalization difficult, and individual efforts to clarify situations over individual cases almost impossible. There appears to be a real need for raising standards of the workers concerned, and for the developing of personal, economic, social and educational domiciliary support of the parents of mentally subnormal and psychically disturbed children.

ACKNOWLEDGMENT

I wish to thank Dr. Ritchie Russell and Dr. A. E. P. Swinson, Physician Superintendent, Pewsey Hospital, for their help in frequent discussions, and for reading over, and commenting on, this paper.

FOLIE À TROIS

CASE REPORT

By

W. G. DEWHURST, B.M., M.R.C.P.
Registrar

and

M. D. EILENBERG, M.B., M.R.C.P., D.P.M.
Senior Registrar
Maudsley Hospital, Denmark Hill, S.E.5

ONLY 16 cases of folie à trois have been reported in the English literature (Wolff, 1957). The present case seems worth recording because of the rarity with which this condition is described and the problems it raises.

FAMILY HISTORY

The persons chiefly involved were:

(1) Helen—aged 60 years—mother.

(2) Kathleen—aged 39 years—daughter of Helen.

(3) David—aged 20 years—illegitimate son of Kathleen.

Helen was born in 1899, of a family free from mental illness. After the death of her father in 1911, Helen's mother remarried in 1914. For 4 years Helen worked in factories, living with her mother and stepfather with whom she had a good relationship. In 1918 Helen (aged 19 years) married a one-eyed soldier, after a courtship of 4 months, and moved with him to his parents' home near Colchester. Helen's husband is a semi-illiterate eccentric individual who, prior to his present illness, was living alone in a caravan, only interested in his "rag and bone" work, and regretted marrying as he was "happy with mother". In 1920 Kathleen was born. Helen, in addition to her household duties, helped in the family off-licence but found the work arduous and her husband's parents mean. Her husband showed little affection towards Kathleen, and the latter was thrown into an increasingly close relationship with her mother, seeing little of her father. Kathleen had no siblings and after an elementary schooling started work on a poultry farm at the age of 14 years and later as a shop assistant.

In 1938 Helen (aged 39 years) decided to part from her husband and moved with Kathleen (aged 18 years) to London. Helen took a job in a factory and Kathleen worked as a shop assistant. Within a few weeks Kathleen met a Mr. W., 9 years her senior, who cohabitated with her. By him Kathleen had an illegitimate child, David, in July, 1939. Helen then decided that Mr. W. was an unstable person, opposed Kathleen's marriage to him and he then left the *ménage*. Kathleen worked fitfully as a shop assistant, interrupted by her psychiatric illness (*vide infra*). In 1951 Helen's mother-in-law bought a lodging

house in North London in Helen's name on condition that she should be looked after until she (the mother-in-law) died. From this time up to the present Helen and Kathleen have run this establishment. Helen occasionally sees her husband, their relations being cool but not unfriendly. In 1959 he was admitted to a psychiatric unit after making a suicidal attempt following the surgical removal of a carcinoma of the rectum.

Pre-Morbid Personalities and Past Psychiatric History

(a) *Helen.* Birth and development revealed no physical or psychological abnormalities. She had few friends, none close; did not trust people easily, spending her leisure in watching television and knitting; always optimistic and energetic, regarded though, by her daughter, as a dreamer with her head in the clouds.

(b) *Kathleen.* She was a friendly girl with many social contacts as an adolescent. Since coming to London at her mother's insistence, she was asocial and unhappy, though the transient relationship with Mr. W. afforded her some happiness. In 1944, at the age of 24 years, she presented at a psychiatric hospital with auditory hallucinations. A diagnosis of schizophrenia was made and treatment advised, but she refused. Thereafter, the hallucinations disappeared but she seldom left the house during the next 12 years.

(c) *David.* As a child he was frightened of the dark, a nail biter and had occasional tempers. He attended school from 5 years to 15 years and since leaving had a poor work record. At the age of 16 years, following his apprehension for sexual offences, he was committed to a Mental Deficiency Colony (I.Q. 70 and M.A. 10 years), being discharged on licence in November, 1957, at the age of 18 years. He had no friends of either sex, helping his grandmother with domestic chores; only leaving the house to buy cigarettes; afraid of crowds with feelings of inferiority and depressive episodes. David was brought up believing Helen was his mother and Kathleen his sister.

History of Present Illness. (This was obtained from the three patients independently. These accounts confirm each other and have here been amalgamated for clarity of presentation.)

In April, 1956, at the instigation of her mother, Kathleen was admitted to hospital with a 2-months history of bizarre somatic sensations, chiefly concerning her skin. Grimacing and schizophrenic thought disorder were noted. She was discharged "improved" after 6 E.C.T.s. In 1957, her mother, Helen, unbeknown to Kathleen, put an advertisement in the matrimonial columns of a newspaper seeking a potential husband for Kathleen. Kathleen was annoyed but then selected from the replies to the advertisement one letter signed by Charles C——. This correspondent had emphasized his avowed sincerity but for this very reason Kathleen became suspicious of the man's good intentions. Nevertheless, she invited him to their house. After a short visit, Kathleen told her mother that she believed the man was a murderer. Her reason for this supposition was based on the fact that both Kathleen and one of the man's alleged victims were wearing scarves. Helen did not accept this idea and dissuaded Kathleen from reporting the matter to the police. David overheard the discussion and thought there must be some truth in Kathleen's beliefs, particularly as the man had then been seen "to wipe his wine glass on the carpet". Kathleen elaborated her delusions which involved ideas of reference based on television, newscasters, newspaper headlines, the police and the

Government. Kathleen was re-admitted to hospital in August, 1958 for 5 weeks when she was found to be deluded, grimacing and possibly hallucinated. On separation from her daughter, Helen developed her own ideas of reference which were added to, following her discussions with Kathleen. Helen later smashed a television set because of the newscaster's comments and shortly afterwards attempted to gas both Kathleen and herself. Helen also reported the "plot" to Scotland Yard in April, 1959. In October, 1959, David, who partially accepted Kathleen and Helen's delusions, complained to them that a newscaster had driven him to kiss a 10-year-old girl and later lodged complaints to Scotland Yard about "being hounded by the Police". As a result of Helen's and David's complaints to the police, a duly authorized officer was called in and arranged admission to the observation ward.

Physical and Mental States of Participants

(a) *Helen.* Physical state normal. Mentally, the patient had paranoid delusions and ideas of reference as described above and refused to accept that she might be unwell. Her mood was placid for the most part though occasionally irritable.

(b) *Kathleen* (not admitted to the observation ward). A woman of attractive appearance who tended to become angry, excited and hostile when discussing her delusions. Ideas of reference were present with complete lack of insight.

(c) *David.* Normal physique but looking younger than his years. Mentally, he was visibly depressed, self-pitying and restless. He spoke excitedly and continually of the events which led to his hospital admission in a rambling but fairly coherent way. He was bewildered by the family delusions, and during his stay expressed the idea that his family was ill and their ideas as "crazy". He believed that people look at him and laugh in the street, but suggests "it might be my imagination". Wechsler-Bellevue, I.Q., 81.

Discharge and Follow-up Note

On discharge Helen returned home to Kathleen, whilst David went to work under the care of his natural father. However, David later returned to Helen and Kathleen's home and the family's delusional ideas and reactions were such that they fled from London and were later admitted to a county mental hospital in early 1960. At that time David was regarded as anti-social and an aggressive person of low intelligence. Helen and Kathleen responded sufficiently to drugs so that both were shortly discharged home.

Discussion

Much confusion exists in the literature on the "folie" syndrome because different entities have been included under these names. If one accepts the classification of Marandon de Montyel (1881) who sub-divided the group into "folie communiquée", "folie imposée" and "folie simultanée", Helen is categorized as "folie communiquée". She showed initial resistance to the delusional ideas but, once accepted, the ideas were retained and uninfluenced by separation. Indeed, their acceptance occurred whilst the inductor (Kathleen) was in hospital. David, on the other hand, when seen by us was a case of "folie imposée" who presented no initial resistance to the delusional ideas and who lost them equally readily after separation. From a clinical point of view the group possesses many of the features commonly noted in the literature. Their

delusions were persecutory in nature, the psychosis schizophrenic in form; aggressive acts occurred (Greenberg, 1956) and their long and intimate association was coupled with a degree of social isolation. The differences which this case presents are that the younger person appeared to induce the elder; the latter developed her psychosis when separation occurred, and the inductor (Kathleen) had a much less dominant and authoritative personality.

The importance of heredity in the "folie" syndrome is controversial. Earlier writers, such as Lasègue and Falret stressed its importance. In "folie communiquée", heredity and predisposition have been considered essential whereas in "folie imposée" they have been regarded as of minor importance. Marandon de Montyel held that there were only two essential causes, namely psychotic predisposition and "morbid impression". Kallman and Mickey (1946) would only include in the category of folie á deux cases showing no blood relationship.

If the concept of the "folie" syndrome is meaningful in terms of a psychotic person communicating or transferring "insanity" to a non-psychotic individual, it seems to the present authors that the recipient must not only accept the delusions of the inductor, but should be free of primary psychotic experiences, and that resolution should follow separation. The continuation or development of the psychosis following separation and the appearance of new psychotic experiences in the supposed recipient seems to suggest that the second individual has developed a psychosis *sui generis*. The inductor may then be seen as a contributory agent but not the sole and essential cause. Thus, in this context, Helen (as distinct from the classical viewpoint presented in the initial paragraph of the discussion) may be considered to have a schizophrenic illness in addition to her daughter, whilst David is more correctly viewed in terms of the true "communicated insanity".

If this view is sustained we suggest that to include "folie communiquée" as a part of a "folie" syndrome which includes "folie imposée" is neither very meaningful nor helpful. We suggest that the term "folie imposée" or true "communicated" psychosis be retained and that a more homogeneous clinical material would result from the exclusion of blood relationship. This view is substantially in agreement with Ropschitz (1957). Thus environmental as distinct from genetic factors could be more clearly evaluated in the aetiology of these psychotic disorders. Because of the doubts thrown upon the essential communication or transference aspect of "folie communiquée" the term "psychosis of association" (Gralnick, 1942) is preferred by the authors at the present stage of knowledge, but is used in a less comprehensive way than the originator intended. It is relatively free from the aetiological implications invested in the classical terminology. The attempt to separate the different entities previously classified under one term clarifies the problems involved and provides thus a necessary step which is an essential pre-requisite for any future studies. It is considered that the condition "folie imposée" restricted to persons not of the same blood relationship would appear to be the most fruitful source of further study for evaluating the significance of environmental factors.

Summary

A case of classical "folie à trois" is reported in a mother, daughter and son. Some of the problems of classification are discussed in the light of the data presented.

Acknowledgments

Acknowledgment is made to Sir Aubrey Lewis, Institute of Psychiatry, The Maudsley Hospital, for permission to publish.

References

Gralnick, A., *Psych. Quart.*, 1942, **16,** 230, 491.
Greenberg, H. P., *J. Ment. Sci.*, 1956, **102,** 772.
Kallman, F. S., and Mickey, J. S., *J. Hered.*, 1946, **37,** 298.
Marandon de Montyel, E., *Ann. Méd.-psychol.*, 1881, **5,** 28.
Idem, ibid., 1894, **19,** 266, 467.
Wolff, S., *J. Ment. Sci.*, 1957, **103,** 355.
Lasègue, C., and Falret, J., "La folie à deux ou folie communique", *Ann. Méd.-psychol.*, 1877, **18,** 321.
Ropschitz, D. H., *J. Ment. Sci.*, 1957, **103,** 589.

NEUROPSYCHIATRIC SYNDROME COMPLICATING OBSTRUCTIVE JAUNDICE OF RECENT ONSET

By

G. W. ASHCROFT, M.B., M.R.C.P.E., D.P.M.

M.R.C. Fellow in Clinical Research

and

P. A. BARKER, M.B., M.R.C.P.E., D.P.M., D.C.H.

Senior Registrar Psychiatrist

Newcastle General Hospital

(*Both authors were formerly Registrars at the Royal Edinburgh Hospital for Mental and Nervous Disorders*)

THIS case is thought to be of interest because neuropsychiatric complications appeared a relatively short time after the onset of obstructive jaundice.

CASE REPORT

A single woman, aged 35, had been in hospital for nine years, suffering from hebephrenic schizophrenia. Treatment with reserpine (15 mg. daily) was started in July, 1957, with some resultant improvement in her mental state, although she continued to show thought disorder and affective blunting.

On 5 April, 1958, she developed painless jaundice. There had been no prodromal symptoms. The serum bilirubin was 4·3 mg./100 ml., alkaline phosphatase 14·6 K.A. Units and thymol turbidity 3 units. Reserpine therapy was discontinued. During the next five days the jaundice deepened, there was persistent vomiting and an occasional elevation of temperature (up to 99·2°). The urine contained bilirubin and excess urobilinogen.

Between 11 and 23 April the jaundice gradually faded, but on 24 April the patient complained of upper abdominal pain and again became markedly icteric. The liver was palpable one finger's breadth below the costal margin. After this, the jaundice fluctuated, but a severe exacerbation with vomiting occurred on 21 May (serum bilirubin 7·4 mg./100 ml., alkaline phosphatase 26·7 K.A. units, thymol turbidity 2·9 units, cephalin-cholesterol flocculation test negative). Again the jaundice subsided only to return on 13 June. On this day the patient became drowsy and developed involuntary movements affecting the left arm and leg. These comprised recurrent attacks of slow, clonic, flapping movements, lasting between 30 seconds and 2 minutes. Consciousness was retained and the patient complained of her inability to prevent the movements. Chlortetracycline 250 mg. 6-hourly was started and the diet was limited to glucose drinks.

At 5 a.m. on 14 June the patient had a grand mal seizure followed by 5 further fits between 5.30 a.m. and 8 a.m. She was given phenobarbitone 1½ gr. (0·1 g.) intravenously at 5.30 a.m., repeated at 8 a.m. At 9.20 a.m. she was deeply unconscious, with widely dilated pupils, and was not responding to painful stimuli. There was a flaccid paralysis of all four limbs, the tendon reflexes were absent and the plantar reflexes flexor. She showed obvious palmar erythema and foetor hepaticus was noticed transiently. The biochemical findings were: serum bilirubin 8·8 mg./100 ml., thymol turbidity 2·4 units, alkaline phosphatase 23 K.A. units, blood urea nitrogen 14 mg./100 ml., blood sugar 176 mg./100 ml., serum sodium 139 mEq/1., potassium 3·4 mEq/1., chloride 90 mEq/1.; prothrombin activity 100 per cent.; C.S.F. —normal pressure, no cells, normal protein. 300 ml. of 50 per cent. dextrose was given intravenously and by 10.30 a.m. there was a slight improvement in the level of consciousness.

Subsequent treatment comprised intravenous fluids, intramuscular penicillin and streptomycin (later replaced by oral neomycin) and parental vitamins. By the following day (15 June) the patient had regained consciousness, and although she remained irritable for a few days with at times clouding of consciousness, there was a steady improvement in her condition, with return of liver function tests to normal. By 19 June the palmar erythema had faded, and by 10 July she was taking a normal diet. An electroencephalogram (EEG) on 8 July was normal apart from a few sharp potentials in the posterior regions. A cholecystogram

(10/7/58) showed multiple gall stones, and at cholecystectomy (19/8/58) the gall-bladder was found to contain a number of small, facetted calculi; several calculi were also removed from the common bile duct.

The patient made a good recovery from her operation and has since shown no evidence of liver disease. Subsequent investigation showed that 4 per cent. of an intravenous dose of bromsulphthalein remained after 52 minutes; a barium swallow revealed no evidence of oesophageal varices; and the EEG was unchanged. 12 g. of ammonium chloride given daily for 17 days (Phillips *et al.*, 5) failed to precipitate any recurrence of neurological symptoms.

Discussion

Most reports of the neuropsychiatric complications of liver disease have concerned patients with acute hepatic necrosis or with long-standing cirrhosis; among the latter are some cases of biliary cirrhosis but the biliary obstruction is usually complete and of many months' duration. Foulk *et al.* (2) mention four cases due to gall-stones but do not state the duration of biliary obstruction. No cases comparable to ours are described in the papers of Adams and Foley (1), Sherlock *et al.* (6), Phear *et al.* (4) or Summerskill *et al.* (7). A case with some clinical features similar to those of our case has, however, been reported by Kushner and Szanto (3). This patient—a chronic alcoholic—had fluctuating jaundice due to a pancreatic carcinoma. On the 80th day of jaundice he developed "convulsive seizures" of the right arm and leg and, five days later, generalized convulsions. At autopsy there was no evidence of hepatic cirrhosis and diffuse changes were found in the brain. These included old fibrotic lesions and recent perivascular haemorrhages and capillary dilatation.

Our patient had obstructive jaundice due to gall-stones, but at no time did liver function tests indicate significant parenchymal liver damage; nor was there any evidence of portal-systemic venous anastomosis. She developed a neuropsychiatric syndrome with involuntary movements, fits and coma ten weeks after the onset of the jaundice, and this appeared to respond to a "hepatic coma regime". She had never previously shown any evidence of epilepsy. It seems possible that her schizophrenia may have been a factor predisposing to the development of the neurological syndrome but we have found no reference to this in the literature.

Summary

This report describes a neuropsychiatric syndrome occurring in a schizophrenic woman who developed obstructive jaundice due to gall-stones. A survey of the literature suggests that such a complication is very unusual in obstructive jaundice of this type.

Acknowledgments

We are grateful to Dr. Elizabeth Robertson, Dr. John Macleod and Mr. A. I. S. Macpherson, the consultants under whom this patient was treated, for their advice; and to Dr. T. A. Munro, Physician Superintendent of the Royal Edinburgh Hospital, for permission to publish.

References

1. Adams, R. D., and Foley, J. M., *Res. Publ. Ass. nerv. ment. Dis.*, 1953, **32**, 198.
2. Foulk, W. T., Butt, H. R., Stauffer, M. H., Baggenstross, A. H., and Gross, J. B., *Gastroenterology*, 1955, **29**, 171.
3. Kushner, D. S., and Szanto, P. B., *J. Amer. med. Ass.*, 1958, **119**, 248.
4. Phear, E. A., Sherlock, S., and Summerskill, W. H. J., *Lancet*, 1955, *i*, 836.
5. Phillips, G. B., Schwarz, R., Gabuzda, G. J., and Davidson, C. S., *New Eng. J. Med.*, 1942, **247**, 239.
6. Sherlock, S., Summerskill, W. H. J., and Dawson, A. M., *Lancet*, 1956, **2**, 689.
7. Summerskill, W. H. J., Davidson, E. A., Sherlock, S., and Steiner, R. E., *Quart. J. Med.*, 1956, **25**, 245.

THE INVESTIGATION OF THE EFFECTS OF PSYCHIATRIC TREATMENT*

By

B. FOX, M.A.

Research Assistant

Psychology Department, Institute of Psychiatry, London

Introduction

The first aim of the study reported in this paper was to check Foulds's finding that claims for the success of a treatment were related to the degree of experimental control which authors exercised in their investigations (77). Foulds, from a selection of papers appearing between 1951 and 1956, showed that five studies (6·9 per cent. of the total) were controlled and claimed success, 15 (20·8 per cent. of the total) were controlled and claimed failure, 43 (59·7 per cent. of the total) were uncontrolled and claimed success and 9 (12·5 per cent. of the total) were uncontrolled and reported failure.

The second aim of the present study was to enquire further into the causes of apparently discrepant outcomes of the same treatments in different studies, even where the studies are scientifically acceptable. This part of the study was suggested by a comment made by Staudt and Zubin (79) that: "In reviewing the vast literature of therapeutic results one finds conflicting reports, ranging from severe scepticism of the various therapies to inordinate enthusiasm for them. Consequently, every clinician can cite a study to support his particular viewpoint on any given therapy".

Procedure

In this study the 1957 volumes of the following journals were examined: *Acta Psychiatrica et Neurologica Scandinavica*, *American Journal of Psychiatry*, *Archives of Neurology and Psychiatry* (*Chicago*), and the *British Journal of Medical Psychology;* the *Journal of Abnormal and Social Psychology*, *Journal of Clinical Psychology*, *Journal of Consulting Psychology*, *Journal of Mental Science*, and *Journal of Nervous and Mental Diseases;* the *Psychiatric Quarterly* and the *Psychological Bulletin.*

For reasons extraneous to this paper, attention was only given to papers using quantified measures, and which were concerned with psychological change in psychiatric patients: 71 of these were found.

These papers were then divided into two groups: those which were scientifically acceptable and those which were not. There were two stipulations for acceptibility: (*a*) the experiment had to be reasonably controlled, either by the use of control groups, "own-control" procedures, or a suitable alternative, and (*b*) the results had to be subjected to an adequate statistical analysis.

* Most of the work reported in this paper was done on the basis of a grant by the Medical Research Council of Great Britain. The work was carried out under the supervision of Dr. M. B. Shapiro, who contributed many of the ideas and formulations appearing in this paper. Acknowledgments are due to Dr. F. Post for his criticisms of the paper.

The Selection of Papers

The method of selecting the papers was as follows: The contents table of each journal was examined. Those articles which, by title alone, were obviously unlikely to have any connection with psychological change in psychiatric patients were eliminated. Any title which suggested the least possibility of relevance to our topic was selected for examination. Any paper, whose irrelevance was not obvious by its title, was given a brief examination before a decision was made as to its inclusion. In this way, of 1,056 papers, in the 11 journals, 232 were selected as being certainly related to our topic.

These papers were then examined and classified into those using quantified methods of estimating psychological change, and those using unquantified ones. Seventy-one papers using quantified methods of measuring psychological change were found. Of these, there were 14 papers (4) (6) (11) (24) (26) (32) (34) (43) (51) (54) (56) (57) (64) (67), which for one reason or another did not present unequivocal findings on the effects of treatment. The remaining 57 papers were classified in the manner shown in Table I.

Criteria of Success and Failure

Before reporting the results, it is necessary to discuss our definitions of success and failure of treatment. Foulds apparently took success to mean that a therapy had proved efficacious in *curing* the patient's illness, and failure to mean that it had not (51). Foulds does not, however, say how he regarded a treatment which had produced a definite but *detrimental* change. In the present study such a change was regarded as a failure, and was classed together with studies which do not report a significant reaction to treatment.

Many of the papers which were examined in the present study were categorized only with great difficulty in terms of success or failure. This is because the variables which were investigated could often be regarded only as one aspect of a patient's total adjustment, or because the measures used had only a hypothetical or attenuated relationship to mental disorder. Even when symptoms were measured, it would be possible to argue about their choice. One cannot, therefore, talk about success or failure as the outcome of such studies: one can only talk of negative and positive results. By "positive" results is meant that the treatment has made a positive contribution to the welfare of the patient—and not that the results were as hypothesized. By "negative" is meant that treatment has made no contribution to the welfare of the patient or has caused deterioration in his or her condition. Authors may, for instance, set out to prove the detrimental effect of a certain therapy, and may succeed in doing so. This, however, is classed in the present paper as a "negative" study, because the contribution to the patient is negative. In this paper, therefore, reference will be made only to "positive" and "negative" outcome, as opposed to "success" and "failure".

Sometimes, a study dealt with several different aspects and effects of a treatment, and reported that the treatment was successful in some ways but actively detrimental in others (68). It was decided, for the first purpose of the study, to accept any partially positive results as "positive", if the authors in summing up claimed a positive value for the treatment; but in the second part both positive and negative aspects were recorded.

It was also found that some studies reported the positive effects of a therapy with one particular type of patient, and negative results of the same therapy with another type (28) (29). If a study took different samples, such as, say,

depressives and schizophrenics, it was counted as "positive" in both parts of the present paper, because we can only expect a treatment to have a limited application, just as in physical medicine we do not expect a treatment to be a panacea for all ills.

Finally, certain studies examine more than one treatment, either simultaneously or comparatively (7) (21) (68). In the first part of the paper these are counted as "positive", if any part or single treatment is positive. In the second part each treatment is counted as positive or negative in its own right. Thus a single study is often recorded more than once.

Foulds made no mention of any of the problems discussed above, so it is difficult to repeat his procedure exactly.

The present study will be relatively superficial, because it is not possible, with such terms as "positive" and "negative", or even "success" and "failure", to give a precise indication of relative values of the different therapies.

TABLE I

Bibliographical Reference Numbers of Papers Reporting Scientifically Acceptable, and Unacceptable Studies with Positive and Negative Results

									N
Positive:									
Acceptable ..	2	9	15	17	19	25	29	33	
	37	41	42	46	47	52	61	62	
	63	65	74						19
Non-acceptable ..	5	7	10	12	20	21	22	23	
	31	35	36	38	39	40	44	48	
	50	68	70	75					20
Negative:									
Acceptable ..	3	8	13	14	16	18	28	45	
	49	53	55	58	60	66	71	72	16
Non-acceptable ..	27	69							2
									57

RESULTS

Acceptability and Outcome

Nineteen (33·3 per cent. of the total) of the studies were "positive" and methodologically acceptable, 20 (35·1 per cent. of the total) were "positive" and unacceptable; 16 (28·1 per cent. of the total) were "negative" and acceptable, and two (3·5 per cent. of the total) were "negative" and unacceptable (see Table I). The outstanding finding in the dearth of unacceptable studies reporting negative outcome, the other categories being fairly equally represented.

A two by two χ^2 analysis of these results show that they are significantly different from chance at $> \cdot 001 < \cdot 005$ level of probability.

TABLE II

Two by Two χ^2 Analysis of Results

	Positive	Negative	Σ	Unclassifiable
Acceptable	19 (5)*	16 (15)	35	14
Unacceptable	20 (43)	2 (9)	22	
	39 (48)	18 (24)	57	

* The figures in brackets are those given by Foulds in his study.
χ^2 for this table=8·54.

The tendency to report positive findings is much higher than the tendency to report negative ones. The χ^2 for this difference is 7·72, which is significant at the $<$ 1 per cent. $>$ 5 per cent. level.

The proportion of acceptable studies is larger than the unacceptable ones, but the difference is not quite significant, $\chi^2=2\cdot9$ (P$=\cdot10$).

Discussion and Conclusions

The present findings confirm Foulds's survey, in so far as outcome and acceptability of experimental design appear to be related. The present study, however, differs from that of Foulds in a number of respects. In the first place, Foulds found that positive studies tended to be uncontrolled, whereas in the present study the "positive" studies were divided fairly equally between "uncontrolled" and "controlled" categories. Secondly, Foulds found that there were more uncontrolled studies than controlled. Our finding is exactly the opposite, though it does not reach an acceptable level of significance. These differences might be due to the possibility that authors who take the trouble to quantify their measures of psychological change, are also more likely to take the trouble to control their experiments and treat them statistically.

There are a number of possible explanations of the main finding, concerning the lack of unacceptable studies reporting negative outcome. Firstly, editors may be inclined to accept articles reporting negative results only if they are properly designed, while their attitude to papers reporting success may be more lenient.

Secondly, authors may be reluctant for a number of reasons to submit papers with negative results, unless they are certain that the results have been demonstrated undisputably. On the other hand, authors who have spent a great deal of trouble on the design of their experiments may be less willing to throw away the results even if they are negative.

Finally, in the absence of evidence obtained from properly selected controls, it might be much easier to convince oneself, albeit honestly, and one's colleagues, that a treatment has been successful.

If methodological acceptability is used as a criterion for the publication of papers, then this should apply equally to studies reporting negative and positive outcomes. It is conceivable that methodologically unacceptable studies might nevertheless be of considerable interest: in this case studies reporting negative outcomes should be as instructive as those reporting positive cases.

Investigation of Conflicting Results

It was decided to include in this part of the study five papers which were omitted from the previous section. These all appeared in 1957, and were all relevant to the topic of our choice, but did not appear in the 11 above-mentioned volumes. They were taken from *Dissertation Abstracts*, which because of its size and coverage of all academic subjects, did not permit the same careful scrutiny which was given to the other 11 journals. It was decided, however, to consider these five papers in this section because they provided useful material for pursuing our second purpose.

The psychological therapies had to be excluded from this survey because of the very different operations covered by this heading. There appeared to be no basis for comparing them. Included under the heading "psychological therapies" are treatments given the following names by their authors: psycho-

therapy, group therapy, activity therapy, attention and adjunctive therapy, and semantic training.

TABLE III

Showing Bibliographical Reference Numbers of Discrepant Studies—Acceptable and Unacceptable

	Positive				Negative			
Therapy	N	Acceptable	N	Non-acceptable	N	Acceptable	N	Non-acceptable	N
Psychological ..	9	9 10 25 33 41 46 65 74 76	4	5 12 35 70	2	59 72 —	—	— — —	15
Chlorpromazine ..	3	1 15 52	6	21 23 39 48 60 75	4	53 73 42 45	—	— — —	13
Pacatal/Mepazine	—	—	1	22	1	3	1	21	3
Meprobamate ..	1	29	1	50	1	71	—	—	3
Hydroxyzine ..	1	63	—	—	1	13	—	—	2
Reserpine	—	—	1	38	3	16 28 55	2	21 27	6
Parentrovite ..	1	37	—	—	—	—	—	—	1
Sparine	—	—	1	40	1	66	—	—	2
Ritalin	—	—	—	—	1	60	—	—	1
Reserpine+Ritalin	1	47	—	—	—	—	—	—	1
Mescaline	—	—	1	44	—	—	—	—	1
Frenquel	—	—	—	—	2	49 58	1	21	3
Meratran	—	—	—	—	1	58	—	—	1
Chlor.+Reserpine	1	62	1	20	—	—	1	21	3
Perphenazine ..	1	42	—	—	—	—	—	—	1
E.C.T.	1	17	3	10 36 68	3	8 14 18	2	68 69	9
Lobotomy	2	2 61	1	31	1	30	—	—	4
Insulin	—	—	1	7	—	—	—	—	1
	21		21		21		7		70
Unclassifiable:			4	6 24 26 32	34	43 51 54	56	57 64 67	
Studies tabulated more than once:			21	42 58 60 61 68					

Superficially, it would seem that Staudt and Zubin's contention is borne out, as an examination of Table III will show. All but one of the 11 kinds of treatment, which were subjected to more than one study, appeared to produce discrepant results when considered merely in terms of the broad and unqualified concepts of "positive" and "negative" outcome, without regard to their acceptability.

An interesting example of this was the discrepancy between the studies of Cronholm and Mollander (14) and Stenbäck *et al.* (68), which appear within a few pages of each other in the same journal. One study reports a deterioration of memory with E.C.T. and the other an improvement.

In order to elucidate the causes of such discrepancies only the acceptable studies were examined. When this was done all the discrepancies turned out to be explicable in terms of differences in: (*i*) the samples; (*ii*) the measures; or (*iii*) the length of periods between test and retest. The details of these studies are

given below. On the three occasions when such discrepancies did not exist there was agreement in the outcome of the studies concerned. The three occasions of such agreement are described below, one under the heading of "E.C.T." (8) (18), and two under the heading of "chlorpromazine" (15) (42) (52) (53).

The discrepancies under each treatment will be dealt with in turn.

Lobotomy. Two studies reported "positive" outcome for this treatment (2) (61), and one reported "negative" results (30). In the first "positive" study, Algeo *et al.* (2) measure changes by the "Sensibility Quotient" and the "Self-Regarding Span" tests. These tests purported to measure the individual's "susceptibility to emotional experience" and his "self-continuity", i.e. the time he spent thinking and talking about himself as a person. The authors studied the immediate effects of lobotomy. The second "positive" study was that of Scherer *et al.* (61), who claimed that, over five years, positive changes occurred in their measures of "functioning efficiency". On the whole, these measures appeared to involve a wide variety of cognitive functions. Thirteen of the 41 measures used showed changes at the 20 per cent. level of significance for the experimental compared with the control group after five years, and of these changes ten were positive.

The "negative" study was by Heller (30) who found that schizophrenic language continued to deteriorate after lobotomy i.e. the intervention of therapy did not lessen progressive deterioration.

The patients in all the above studies were schizophrenics. It is clear from the above descriptions that the psychological functions measured, appeared, on the surface, to be very different from each other in content. They might have had underlying factors in common, but this is a matter of fact which would have to be demonstrated by appropriate correlational studies. The most comparable measures are the "schizophrenic" language of Heller and the vocabulary used by Scherer *et al.* Even here the differences seem to be great, the former author being concerned with idiosyncrasies of schizophrenic language such as rate of speech, neologisms, speech melody, and articulation, whilst Scherer *et al.* are merely concerned with the accuracy of verbal definition.

E.C.T. One study reported a positive outcome and three, negative outcomes. The "positive" study, reported by Dana (17) used several M.M.P.I. scales. The experimental group changed significantly on some of the scales (Schizophrenia, Mania, Psychotic Triad, Prognosis for Shock and Mania Obvious), and there were significantly more changes, both large and small, for the experimental group as compared with the controls. The post-treatment measures were made immediately after the cessation of therapy, and the diagnoses of the patients were not specified.

Agreement of outcome was found in the negative results of Brill *et al.* (8) and Du T. de Wet (18), who, using similar kinds of behavioural rating scales, found no differences in improvement between their experimental and control groups. (The scales involved items rating characteristics such as "delusions", "excitement", "emotionality", "psychotic behaviour" and "anxiety"). In the first study the sample was made up of a mixture of different diagnostic categories, with a preponderance of schizophrenics, and in the second study schizophrenics were the subjects. In both studies measures were made before the beginning and immediately after the cessation of treatment. The third negative study reported by Cronholm and Mollander (14) found changes immediately after the second electroshock, in terms of intellectual and memory deterioration. They also took patients from a mixture of diagnostic categories.

Criteria for improvement in the various studies did not overlap, except in the case of Brill *et al.* (8) and Du T. de Wet (18) whose results were, however, in accord. None of the samples were exactly described, except in the case of Du T. de Wet's study where the patients were schizophrenic.

Hydroxyzine. One positive and one negative study have been reported for this drug. The positive study, by Segal and Tansley (63) used a behavioural rating scale measuring such functions as activity, application and progress, on a sample of maladjusted educationally subnormal children during the course of hydroxyzine therapy.

The negative study reported by Craft (13) finds the drug ineffective with mentally defective patients with I.Q.s round about 30 using a behavioural rating scale very similar in kind to the one used in the study above. His subjects, a mixture of adults and children, however, were of very low intelligence, and undoubtedly far inferior to those of Segal and Tansley. Thus samples were not comparable.

Meprobamate. One positive and one negative study have been reported. The discrepancy in claims for this drug, as made by Heller (29) and Tucker *et al.* (71) could well be due to the differences in their samples. The former achieved successful results on dysthymic neurotic patients, and the latter was unsuccessful with schizophrenics. Further details are not given here because this in itself could be a sufficient cause for the discrepancy in result.

Chlorpromazine. Three studies claimed positive effects for this drug and four were negative. Agreement in outcome appears in the results of Cutler *et al.* (15) and Porteus (52). Both studies report that chlorpromazine was effective when results were measured in terms of behavioural improvement. Rating scales of both authors were similar in nature, measuring a variety of symptoms from aggression and hallucinations to work and activity. Patients in both studies were, for the most part, schizophrenic, though a small proportion of other diagnoses seem to have been included in the samples. In both studies retesting took place at the end of the course of treatment.

Abrams (1) claimed an improvement in intellectual ability on some of the Wechsler-Bellevue subtests, as well as behavioural improvement following chlorpromazine.

There is agreement between the studies of Porteus *et al.* (53) who found that a decrease in Maze ability followed chlorpromazine treatment, and that of Mason-Browne (42), who found a trend in the same direction. The evidence of the latter author was too briefly laid out for detailed evaluation. Whitehead (73) failed to find any changes in learning ability.

In the last four studies described above, the patients were predominantly schizophrenic and retesting was carried out immediately after the cessation of treatment.

Merry *et al.* (45) found chlorpromazine ineffective on patients suffering from chronic neurotic tension. Their tests, to some extent, involved intellectual ability, as the authors themselves say. They are "Write-a-Story" tests, scored for speed, latency, and length and richness of story.

Discussion and Conclusions

Four conclusions emerge from this part of the investigation. Firstly, one should expect agreement in the outcomes of different experiments on the effects of a particular treatment, only if all the experiments: (*i*) use the same criteria and methods of measuring them; (*ii*) use psychologically comparable subjects;

and (*iii*) use the same periods between testings. Secondly, apparently contradictory findings resulting from studies which are not strictly comparable need not be regarded as being discrepant, but could be regarded rather as the outcome of a constellation of therapeutic effects. In fact, their further confirmation and investigation might provide useful information about the nature of the treatment concerned. For example, it might be useful to find out why chlorpromazine improves behaviour as measured by a particular rating scale and impairs performance on the Porteus Maze. Thirdly, investigators should examine the relevant literature before embarking on a study of their own. This would help to provide us with exact replications of previous studies. Fourthly, it would seem that, in our present state of knowledge, research into therapy must be preceded by appropriate validation studies of the measures of psychological variables and of the criteria for the selection of subjects. If one wants to investigate a particular treatment, say, of schizophrenics, one must have reproducible and validated criteria of schizophrenia. Likewise, if one wants to treat retardation. The importance of this consideration is illustrated by the finding of Shapiro *et al.* (78) who report that different types of tests of psychomotor speed differed in their relation to nosological category and in their reaction to experimental manipulation. The preliminary validation of criteria and measures might slow down the rate of publication; but it would probably speed up the rate of advancement of our knowledge.

Summary

This paper reports a study of the literature on the effects of treatment. All the papers, which dealt with the effects of treatment and used quantified measures of psychological change (numbering 57), appearing in eleven journals for the year 1957, were tabulated.

The following findings emerged:

(*i*) Sixteen of the 18 studies with a negative outcome were methodologically acceptable, while the other two were not. The studies with a positive outcome were evenly divided.

(*ii*) Significantly more "positive" than "negative" studies were found.

(*iii*) Apparent discrepancies in the outcomes of acceptable studies of the same treatments were found to be explicable in terms of differences (*a*) in criteria and methods of measurement, (*b*) in samples used, and (*c*) in the length of periods between measurements.

The implications of these findings for future research are discussed.

References

1. Abrams, J., "Therapeutic Value of Chlorpromazine in Effecting certain Psychological Changes", *Dissert. Abstr.*, 1957, **17,** 589.
2. Algeo, N. B., and Pullen, M. S., "Personality Changes following Transorbital Lobotomy", *J. Clin. Psychol.*, 1957, **13,** 308.
3. Baker, A., and Thorpe, J. G., "The Placebo Response", *Arch. Neur. Psychiat.*, 1957, **78,** 57.
4. Bauer, R. W., and Johnson, D. G., "The Question of Deterioration in Alcoholism", *J. Consult. Psychol.*, 1957, **21,** 296.
5. Beck, S. J., and Molish, H. B., "Course in the Individual Patient as Traced in the Six Schizophrenias", *J. Nerv. Ment. Dis.*, 1957, **125,** 403.
6. Beilin, H., "Prediction of Adjustment over a Four Year Interval", *J. Clin. Psychol.*, 1957, **13,** 270.
7. Boling, L., Ryan, W., and Greenblatt, M., "Insulin Treatment of Psychotics", *Amer. J. Psychiat.*, 1957, **113,** 1009.

8. Brill, N. Q., Crumpton, E., Eiduson, S., Grayson, H. M., Hellman, L. I., Richards, R. A., Strassman, H. D., and Unger, A., "Investigation of the Therapeutic Components of E.C.T.", *ibid.*, 1957, **113,** 997.
9. Brown, C. C., "Changes in Avoidance Conditioning following Psychotherapeutic Treatment", *J. Nerv. Ment. Dis.*, 1957, **125,** 487.
10. Browne-Mayers, A. N., Henley, T. F., and Ostwald, P. F., "Grand Mal Convulsions following more than 150 E.C.T.s", *Psychiat. Quart.*, 1957, **31,** 109.
11. Cartwright, D. S., and Roth, I., "Success and Satisfaction in Psychotherapy", *J. Clin. Psychol.*, 1957, **13,** 20.
12. Cohen, S. I., Silverman, A. J., Zuidema, G., and Lazal, C., "Psychotherapeutic Alteration of Physiological Stress Responses", *J. Nerv. Ment. Dis.*, 1957, **125,** 112.
13. Craft, M., "Tranquillizers in Mental Deficiency", *J. Ment. Sci.*, 1957, **103,** 855.
14. Cronholm, B., and Molander, L., "Memory Disturbance after E.C.T.", *Acta. Psychiat. Neurol. Scand.*, 1957, **32,** 280.
15. Cutler, R., Monroe, J. J., and Anderson, T. E., "Effects of Tranquillizers on Pathological Activity of Psychotics. I—Chlorpromazine", *Arch. Neurol. Psychiat.*, 1957, **77,** 616.
16. *Iidem*, "Effects of Tranquilizers on Pathological Activity in Psychotics. II—Reserpine", *ibid.*, 1957, **78,** 61.
17. Dana, R. H., "M.M.P.I. Performance and E.C.T.", *J. Clin. Psychol.*, 1957, **13,** 250.
18. De Wet, J. S. Du T., "Evaluation of a Common Method of Convulsive Therapy in Bantu Schizophrenics", *J. Ment. Sci.*, 1957, **103,** 739.
19. Dittes, J., "Galvanic Skin Response as a Measure of Patients' Reactions to Therapists' Permissiveness", *J. Abn. Soc. Psychol.*, 1957, **55,** 295.
20. Ellsworth, R. B., and Clark, L. D., "Prediction of Response of Chronic Schizophrenics to Drugs", *J. Clin. Psychol.*, 1957, **13,** 59.
21. Feldman, P. E., "Clinical Evaluation of Pacatal", *Amer. J. Psychiat.*, 1957, **114,** 143.
22. *Idem*, "A Comparative Study of Various Ataractic Drugs", *ibid.*, 1956–57, **113,** 589.
23. *Idem*, "Two Year Fate Study of Thorazine Treated Patients", *ibid.*, 1957, **114,** 237.
24. Foundeur, M., Fixsen, C., Triebel, W. A., and White, M. A., "Post-partum Mental Illness", *Arch. Neurol. Psychiat.*, 1957, **77,** 503.
25. Frank, J. D., Gliedman, L. H., Imber, S. D., Nash, E. H., and Stone, A. R., "Why Patients Leave Psychotherapy", *ibid.*, 1957, **77,** 283.
26. Gordon, M. H., Lindley, S. B., and May, R. B., "A Criterion Measure of Within-Hospital Change in Psychiatric Illness", *J. Clin. Psychol.*, 1957, **13,** 145.
27. Gore, C. P., Egan, G. P., and Walton, D., "The Place of Reserpine in the Treatment of Chronic Psychotics", *Amer. J. Psychiat.*, 1957, **114,** 333.
28. Hauck, P., Phillips, H., and Armstrong, R., "The Effects of Reserpine on Psychotics of Varying Degrees of Illness", *J. Clin. Psychol.*, 1957, **13,** 188.
29. Heller, G. C., Walton, D., and Black, D. A., "Meprobamate in the Treatment of Tension States", *J. Ment. Sci.*, 1957, **103,** 581.
30. Heller, E., "Language Before and After Lobotomy", *Dissert. Abst.*, 1957, **17,** 2086.
31. Hill, D., Pond, D. A., and Falconer, M. A., "Personality Changes following Temporal Lobectomy for Epilepsy", *J. Ment. Sci.*, 1957, **103,** 18.
32. Hill, H. E., Belleville, R. E., and Wikler, A., "Motivational Determinants in Modification of Behaviour by Morphine and Pentobarbital", *Arch. Neur. Psychiat.*, 1957, **77,** 28.
33. Imber, S. D., Frank, J. D., Nash, E. H., Stone, A. R., and Gliedman, L. H., "Improvement and Amount of Therapeutic Contact: An Alternative to the Use of No-Treatment Controls in Psychotherapy", *J. Consult. Psychol.*, 1957, **21,** 309.
34. Kalis, B. L., and Bennett, L. F., "The Assessment of Communication: the Relation of Clinical Improvement to Measured Changes in Communicative Behaviour", *ibid.*, 1957, **21,** 10.
35. Kelman, H. C., and Parloff, M. B., "Inter-relation Among Three Criteria of Improvement in Group Therapy", *J. Abn. Soc. Psychol.*, 1957, **54,** 281.
36. King, P., "A Statistical Comparison of Two Methods of E.C.T.", *Amer. J. Psychiat.*, 1957, **114,** 555.
37. Krawiecki, J. A., Couper, L., and Walton, D., "The Efficacy of Parentrovite in the Treatment of Senile Psychotics", *J. Ment. Sci.*, 1957, **103,** 601.
38. Lehman, E., Haber, J., and Lesser, S. R., "The Use of Reserpine in Autistic Children", *J. Nerv. Ment. Dis.*, 1957, **125,** 351.
39. Lesse, S., Malitz, S., and Hoch, P., "Chlorpromazine Therapy in Private Practice", *ibid.*, 1957, **125,** 25.
40. *Idem*, "An Evaluation of Promazine Hydrochloride in Psychiatric Practice", *Amer. J. Psychiat.*, 1957, **113,** 984.
41. Levine, D., "Differential Effects of Factors in an Activity Program", *ibid.*, 1957, **114,** 532.
42. Mason-Browne, N. L., "Perphenazine—A Drug Modifying Consciousness", *ibid.*, 1957, **114,** 173.
43. McAdam, W., and Robinson, R. A., "Prognosis in Senile Deterioration", *J. Ment. Sci.*, 1957, **103,** 821.

44. Merlis, S., "The Effects of Mescaline Sulfate in Chronic Schizophrenia", *J. Nerv. Ment. Dis.*, 1957, **125,** 432.
45. Merry, J., Pargiter, R. A., and Munro, H., "Chlorpromazine and Chronic Neurotic Tension", *Amer. J. Psychiat.*, 1957, **113,** 988.
46. Mundy, L., "Therapy with Physically and Mentally Handicapped Children", *J. Clin. Psychol.*, 1957, **13,** 3.
47. Niswander, G. D., Haslerud, G. M., Brody, N., and Casey, T. M., "Reserpine and Ritalin—Effects on Socialization and Activity", *J. Nerv. Ment. Dis.*, 1957, **125,** 51.
48. Pate, W. H., "Chlorpromazine Therapy following Transorbital Lobotomy", *ibid.*, 1957, **125,** 44.
49. Peak, E. C., Canestrari, R. E., and Roebuck, B. E., "Effects of Frenquel on Chronically Disturbed Patients", *Amer. J. Psychiat.*, 1957, **113,** 653.
50. Pennington, V., "The Use of Miltown with Psychotic Patients", *ibid.*, 1957, **114,** 457.
51. Porteus, S. D., "Maze Test Reactions after Chlorpromazine", *J. Consult. Psychol.*, 1957, **21,** 15.
52. *Idem*, "Specific Behavioural Changes following Chlorpromazine", *ibid.*, 1957, **21,** 257.
53. *Idem* and Barclay, J. E., "A further note on Chlorpromazine", *ibid.*, 1957, **21,** 297.
54. Rashkis, H., and Smarr, G. R., "Psychopharmacotherapeutic Research", *Arch. Neurol. Psychiat.*, 1957, **77,** 202.
55. *Iidem*, "Drug and Milieu Effects on Chronic Schizophrenics", *ibid.*, 1957, **78,** 89.
56. Robertson, M. H., "A Comparison of Client and Therapist Ratings on Two Psychotherapeutic Variables", *J. Consult. Psychol.*, 1957, **21,** 110.
57. *Idem*, "Change and Receptiveness to Psychotherapy", *ibid.*, 1957, **21,** 498.
58. Rosner, B. S., Fierman, L. B., and Kramer, J. F., "A Clinical Evaluation of Meratran and Frenquel on Chronic Psychotics", *Amer. J. Psychiat.*, 1957, **113,** 993.
59. Ryan, T., "Effects of Attention and Various Adjunctive Therapy Programs on Chronic Schizophrenics", *Diss. Abst.*, 1957, **17,** 810.
60. Salisbury, B. J., and Hare, E. H., "Ritalin and Chlorpromazine in Chronic Schizophrenia", *J. Ment. Sci.*, 1957, **103,** 830.
61. Scherer, I. W., Klett, C. J., and Winne, J. F., "Psychological Changes over a Five Year Period following Bilateral Prefrontal Lobotomy", *J. Consult. Psychol.*, 1957, **21,** 291.
62. Schmidt, K. E., "Combined Treatment with Chlorpromazine and Reserpine", *J. Ment. Sci.*, 1957, **103,** 200.
63. Segal, L. J., and Tansley, A. E., "Clinical Trial of Hydroxyzine (Atarax) on a Group of Maladjusted E.S.N. Children", *ibid*, 1957, **103,** 677.
64. Semans, C. B., "The Use of the Semantic Differential with Lobotomized Psychotics", *J. Consult. Psychol.*, 1957, **21,** 264.
65. Semon, R. G., and Goldstein, N., "The Effectiveness of Group Psychotherapy with Chronic Schizophrenics and an Evaluation of Different Therapeutic Methods", *ibid.*, 1957, **21,** 317.
66. Sibilio, J. P., Andrew, G., Daw, D., Moore, K. B., and Stehman, V. A., "Treatment of Chronic Schizophrenics with Promazine Hydrochloride", *Arch. Neurol. Psychiat.*, 1957, **78,** 419.
67. Standal, S. W., and Vander Veem, F., "Length of Therapy in Relation to Counselor Estimates of Personal Integration", *J. Consult. Psychol.*, 1957, **21,** 1.
68. Stenbäck, A., Viitamäki, R. O., and Kukkonen, S., "Personality Changes in E.C.T.", *Acta Psychiat. Neurol. Scand.*, 1957, **32,** 345.
69. *Iidem*, "Psychological Studies on a Patient who Received 441 E.C.T.s", *ibid.*, 1957, **32,** 473.
70. Thorne, F., "An Evaluation of Eclectically Orientated Therapy", *J. Consult. Psychol.*, 1957, **21,** 459.
71. Tucker, K., and Wilensky, H., "Clinical Evaluation of Meprobamate in Chronic Schizophrenics", *Amer. J. Psychiat.*, 1957, **113,** 698.
72. Tucker, H., Lewis, R. B., Martin, G. L., and Over, C. H. R., "Effectiveness of Closed-Circuit Television as a Medium for Therapy of the Mentally Ill", *Arch. Neurol. Psychiat.*, 1957, **77,** 57.
73. Whitehead, W., "Effects of Chlorpromazine on Learning Tasks and Verbalized Social Adaptation", *Dissert. Abst.*, 1957, **13,** 9.
74. Wilcox, G. T., and Guthrie, G. M., "Changes in Adjustment of Institutionalized Female Defectives following Group Psychotherapy", *J. Clin. Psychol.*, 1957, **13,** 9.
75. Winckelmann, N. W., "An Appraisal of Chlorpromazine", *Amer. J. Psychiat.*, 1957, **113,** 961.
76. Yormak, B., "Behavioural Changes following Semantic Training", *Dissert. Abst.*, 1957, **17,** 402.

Other References

77. Foulds, G., "Clinical Research in Psychiatry", *J. Ment. Sci.*, 1958, **104,** 259.
78. Shapiro, M. B., Kessell, R., and Maxwell, A. E., "Speed and Quality of Psychomotor Performance in Psychiatric Patients", *J. Clin. Psychol.*, 1960, **16,** 266.
79. Staudt, V., and Zubin, J., "Evaluation of Somatic Therapies in Psychiatry", *Psychol. Bull.*, 1957, **54,** 171.

AN EVALUATION OF THE FELDMAN PROGNOSIS SCALE FOR SHOCK THERAPY*

By

D. BANNISTER, B.A., Dip.Psych., Ph.D.

Senior Psychologist
Bexley Hospital, Kent

and

H. R. BEECH, B.A., Dip.Psych., Ph.D.

Lecturer in Psychology
Institute of Psychiatry, London

Introduction

Feldman (1951) published a scale for predicting the response of patients to E.C.T. and insulin coma therapy. Using only Minnesota Multiphasic Personality Inventory profiles meeting stated requirements (at least one elevated scale, moderate F scale scores, etc.) he carried out an item analysis of the M.M.P.I. responses of 42 patients who had responded well to shock therapy and 42 patients who had remained unimproved (psychiatrists' ratings). He derived a 52-item scale, scored as an additional M.M.P.I. scale and labelled Ps, high scores indicating poor prognosis. This he cross-validated on a further 100 patients (categorized as recovered, improved or unimproved) and all categories were well discriminated by Ps scale scores.

Pumroy and Kogan (1958) used the Feldman Ps scale (again within the administration of the total M.M.P.I.) as one of a series of prognosis scales given to 23 male patients about to receive E.C.T. and later categorized as Improved or Unimproved by their psychiatrists. They found no significant relationship between their validating criterion and Ps scale scores, but they did not report whether or not their M.M.P.I. profiles met Feldman's requirements.

Roberts (1959), while assessing the prognostic value of a number of physiological measures, gave the *extracted* 52 items of the Ps scale to 41 female patients who were later assessed (1 and 3 months after E.C.T.) as improved or unimproved on a "symptom score basis". No significant relationship was found between Ps scores and symptomatic response as assessed. In this study it is impossible to say whether the full M.M.P.I.s, had they been taken, would have met Feldman's requirements. In considering the literature it should be noted that Roberts mis-reported a later paper by Feldman (1958) as having "modified both the scale and also claims for its predictive value". The 1958 paper reported a new scale designed to evaluate (not prognosticate) the effects of shock therapy. This evaluation of shock therapy (EVS) scale in no way represents a modification

* The authors' thanks are due to the Physician Superintendent, Dr. M. Radzan, and the medical staff of Bexley Hospital for assistance in compiling data for this study.

of the Ps scale and Feldman's comments on its limitations do not refer to the Ps scale.

Gouws (1961) carried out a validational study on 60 patients whose M.M.P.I. profiles met Feldman's requirements (termed "elevated" profiles) and a further 34 patients with M.M.P.I. profiles which did not meet Feldman's requirements (unelevated profiles). The dichotomous criterion of improvement was:

Improved="improved" rating by psychiatrist on leaving hospital and no re-admission to any hospital over the next five years.

Unimproved="unimproved" rating by psychiatrist on leaving hospital *or* "improved" rating but re-admitted to hospital within five years.

For the first group of 60 (elevated profiles) the Ps scale scores differentiated significantly but with higher overlap than was obtained in Feldman's original study; the second group of 34 (unelevated profiles) were not significantly differentiated into improved and unimproved by the Ps scores. This suggests that Feldman's profile requirements need to be met in comparative validational studies.

Present Study

With the aim of further assessing the validity of the Feldman Ps scale an experiment was carried out as follows:

A population of 33 mental hospital patients who had given M.M.P.I. profiles which met Feldman's requirements from 1 to 21 days before receiving E.C.T. or insulin therapy was used. Follow-up data covering a period of (on average) 6 months from cessation of treatment was assembled. Each of the present authors independently rank ordered the population for response to treatment on the basis of the following instructions. "Allot the patients to four categories which are ranked in descending order as follows:

(*i*) Left hospital after treatment and returned to work.

(*ii*) Left hospital after treatment but has not returned to work.

(*iii*) Remained in hospital after treatment.

(*iv*) Remained in hospital after treatment and has since been leucotomized.

Within these four groups' rank order the patients, on the basis of the degree of improvement, indicated by the day to day progress assessments made by the psychiatrists and entered in the case notes."

Working independently to these agreed instructions the authors prepared their rankings, and the rank order correlation (Spearman's rho) between the two was $+\cdot 93$. This interjudge correlation was considered high enough to justify using the second author's rankings (without combination) as validating criterion and to indicate that the criteria of ranking were adequately defined.

It seemed to the authors that, as a judgmental task, comparisons between cases are easier to make than allotments to absolute categories whose boundaries are inevitably ambiguous. This and the use of a series of categories which defined broad rank position probably accounts for the high interjudge agreement.

A rank order correlation was run between the ranking by order of response to treatment and ranking by order of Feldman Ps scores. Spearman's rho for this was $-0\cdot 05$. Thus there appears to be no significant relationship between Feldman Ps scores and response to treatment as here assessed.

Content of the Feldman Scale

Before comparing the results of the various validational studies a brief investigation of the content of the Feldman Ps scale is reported.

Using 102 M.M.P.I. profiles which met Feldman's requirements a factor analysis of the 52 scale items by Principal Component Analysis was carried out. Three factors emerged accounting for 11·70, 5·94 and 4·81 per cent. of the variance respectively. These factors proved impossible to identify in the form in which they emerged, in addition the third factor had only three rather diverse items exclusively loaded on it. It was possible to achieve apparently meaningful rotation which suggested that Factor I was concerned mainly with items expressive of social hostility while Factor II was characterized by items expressive of social anxiety. Such identification is necessarily speculative and might well fail to replicate. It is, however, broadly consistent with Feldman's general characterization of the scale which he deemed primarily concerned with interpersonal relations. It should be noted that Gouws (1961) in the study previously mentioned found that the Ps scale for his sample correlated +·84 with an Adjustment scale (Fulkerson, 1957) dealing, in part, with the quality of interpersonal relations and +·65 with an Aquiescence scale (Fulkerson, 1958) indicative of a tendency to agree although these three M.M.P.I. scales have relatively few items in common. Both the Adjustment scale and the Aquiescence scale discriminate "improved/unimproved" patients as efficiently as the Ps scale. This and the small amount of variance accounted for by the factor analysis tend to confirm Gouws' suggestion that the "propensity to improve" (a general factor hypothesized by Feldman) may well be a complex entity.

The fact that Feldman found that his Ps scale predicted response to E.C.T. and insulin therapy equally well and response to brief psychotherapy to a significant degree, coupled with Gouws' finding that for his sample the scale predicted response to supportive care as well as response to E.C.T. suggests that it is general prognosis rather than capacity to respond to a specific treatment which is related to the scale.

In parenthesis it should be noted that Feldman's (1958) *evaluation* of shock therapy scale (EVS) which was derived from an item analysis of pre- and post-shock M.M.P.I. responses primarily concerns reported improvements in bodily feelings rather than improved reactions to interpersonal relationships. Thus the nature of the psychological change brought about by shock therapy may not correspond with the precise features prognosticating a good response.

Comparison of Studies

Of the five studies (including the present one) reported to date, two suggest that the Ps scale is to some degree valid and three report no evidence of validity. At least two variables can be examined in relation to these contrasting results. The diagnostic composition of the samples (particularly the ratio of recovered to non-recovered patients within each diagnostic category) and the nature of the response assessment used as validating criterion.

Diagnostic Composition of Samples

Both Feldman's groups (criterion and test) consisted largely of Depressives who responded well to treatment and Schizophrenics and Psychoneurotics who did not respond well. Indeed this biased distribution is so marked that had

Feldman merely predicted recovery for each Depressive and non-recovery for each Schizophrenic or Neurotic he would have achieved a chi-square significant at well beyond the 1 per cent. level of confidence. Feldman points out that the mean Ps score of all Schizophrenics and all Neurotics was significantly higher than the mean Ps score of all Depressives. He rightly claims that since *within* each diagnostic group the "improved" are significantly discriminated from the "unimproved" his overall significant discrimination cannot be attributed to his diagnosis/recovery rate proportions. However, it is clear that his discrimination was *improved* by the particular diagnosis/recovery rate proportion of his sample. A sample of Depressives ("naturally" lower scorers) who recover and Schizophrenics/Neurotics ("naturally" higher scorers) who fail to recover maximizes score differences between recovered and unrecovered groups where high scores indicate a bad prognosis.

Pumroy and Kogan (1958) do not report the diagnostic composition of their sample but Roberts's (1959) sample consisted entirely of Depressives—thus minimizing the hypothesized effect. Gouws' (1961) sample consisted of Depressives and Schizophrenics who almost equally distributed themselves into recovered and non-recovered and Neurotics who were roughly in ratio of two recovered for every one who failed to recover. Gouws does not report his Ps scores by diagnostic group but if the tendency for all Depressives (recovered and non-recovered) to give lower scores held good then his distribution would have minimized his discrimination levels (which were admittedly lower) rather than maximized them as was the case in Feldman's study.

In the present study the population consisted of 16 Depressives with 7 recovered and 9 unimproved (defining recovered and improved as the top and bottom half of the response rank ordering respectively) and 17 Schizophrenics/Neurotics with 9 recovering and 8 not. Again the proportion of recovered to non-recovered in the diagnostic groups does not favour discrimination. The mean Ps scores for the two groups are Depressives 19·45, S.D. 4·86 and others 21·12, S.D. 9·43. This difference is not statistically significant but the direction suggests that bias by diagnosis/recovery rate proportions was operating to diminish discrimination.

The Nature of the Validating Criterion

The second variable which might have affected the comparative results of the studies is the character of the validating criterion. Two studies used psychiatric ratings of recovery, one used ratings of specific symptoms, one psychiatric ratings plus long-term re-admission data and the present study rank ordering by psychologist against overall defined categories. Windle's (1952) exhortation that "it is necessary to bear in mind that unless measures of outcome are highly correlated, the meanings of prognosis in different studies will differ" seems to have gone unheeded.

The aspect of the validating criterion which, on face inspection, seems most likely to relate to the varying validational fortunes of the Ps scale is the length of time elapsing between treatment and assessment of response. In Feldman's study the assessment seems to have been based on follow-up data taken up to approximately one year after treatment. In Gouws' study, the only one which confirmed Feldman's findings, the recovery assessment was based on a five-year follow up. In the three studies which failed to confirm the scale's validity assessment was made one month after treatment (Pumroy and Kogan), one and three months after treatment (Robertson) and, on average, six months after treatment

(present study). It is possible, therefore, that the Ps scale is predictive of long-term rather than immediate response to treatment and that short-term validating criteria tend to minimize the scale's effectiveness.

Conclusions

Any definitive attempt to evaluate the Feldman's Ps scale would seem to require an experimental design which permitted the analysis of the scale scores in relation to diagnostic group/recovery rate ratio, the effect of varying time lapses between treatment and assessment of response and the effect of varying techniques of response assessment (psychiatric ratings, symptom ratings, categories based on subsequent work and re-admission history and so forth). Concomitantly, attempts to investigate the psychological content of the scale might utilize Gouws' technique of correlating with other scales chosen in the light of the explanatory hypotheses set up. From a theoretical point of view it might be rewarding to investigate the relationship between responses predicting recovery and responses changing with recovery since, as Feldman suggests in his 1958 study, this might throw light on the nature of what is meant by "getting better" —the differential effects of somatic and psychological treatments might be investigated in this way.

Should the scale eventually prove to have some degree of validity it would still be necessary to establish that it *added* to current psychiatric prognostic methods before its introduction as a clinical tool could be justified.

However, it seems clear, since three of the four subsequent studies failed to repeat Feldman's findings and the fourth study found increased overlap between recovered and non-recovered groups, that the Ps scale is not yet proven to the point at which it can be accepted as a workable clinical tool.

However, in view of the significant finding of Gouws' study (which seems the most thorough of the four) further work on the scale seems justified. Particularly since an objective method of assessing prognosis would seem, from a clinical psychologist's point of view, a more relevant contribution to the treatment of the patient than current diagnostic testing practices.

Summary

1. Thirty-three patients were given the Feldman Ps scale before shock therapy and rank ordered for their degree of improvement approximately six months after treatment. No significant relationship was found between degree of recovery and Ps scale scores.

2. Explanations of the varying validational fortunes of the Ps scale were suggested. The two primary factors thought to vary in relation to degree of discrimination found in the varying studies were diagnostic group/recovery rate proportions and the varying time interval between treatment and assessment of degree of recovery.

3. Comments were made on the possible psychological content of the Ps scale in the light of previous studies and a factor analysis carried out by the authors—the primary factors emerging concerned social hostility and social anxiety but only a small proportion of the variance was accounted for by identifiable factors.

4. Though the scale was not regarded as a proven clinical tool it is thought that further investigation was desirable and a broad experimental approach is outlined.

References

FELDMAN, M. J., "A prognostic scale for shock therapy", *Psychol. Monogr.*, 1951, **65,** No. 10.
Idem, "An evaluation scale for shock therapy", *J. Clin. Psychol.*, 1958, **14.**
FULKERSON, S. C., "Adaptability screening of flying personnel research on the Minnesota Multiphasic Personality Inventory", School of Aviation Medicine, U.S.A.F., Report No. 57–106, July, 1957.
Idem, "An Aquiescence key for the M.M.P.I.", School of Aviation Medicine, U.S.A.F., Report No. 58–71, July, 1958.
GOUWS, D. J., "Prediction of relapse for psychiatric patients", *J. Consult. Psychol.*, 1961. (To be published.)
PUMROY, D. K., and KOGAN, W. S., "A validation of measures that predict the efficacy of shock therapy", *J. Clin. Psychol.*, 1958, **14.**
ROBERTS, J. M., "Prognostic factors in the electroshock treatment of depressive states. II. The application of specific tests", *J. Ment. Sci.*, 1959, **105,** No. 440, pp. 693, 703.
WINDLE, C., "Psychological tests in psychopathological prognosis", *Psychol. Bull.*, 1952, **49,** No. 5.

PRELIMINARY INVESTIGATIONS OF THE EFFECTS OF SERNYL UPON COGNITIVE AND SENSORY PROCESSES

By

H. R. BEECH, B.A., Dip.Psych., Ph.D.

BRIAN M. DAVIES, M.D., M.R.C.P., D.P.M., D.C.H.

and

F. S. MORGENSTERN, M.A., B.M., B.Ch., D.P.M.

from the Bethlem Royal and Maudsley Hospitals

In a previous paper, Davies and Beech (4) presented data obtained from both clinical observations and psychological tests on normal subjects under the influence of Sernyl. In that paper an account was given of the chemical constitution and action of the drug. It is not necessary to say more here than that this compound is a synthetic cyclohexylamine derivative that was introduced into anaesthetic practice because of its ability to produce analgesia without loss of consciousness. It appears to act mainly at the thalamic level and produces changes in the reception of sensory stimuli. Post-operatively, however, psychiatric disturbances were common and the use of the drug in anaesthetic practice was curtailed. Our interest in Sernyl has centred upon its psychotomimetic effects and its possible mode of action. It has, in fact, been suggested that normal individuals under the influence of Sernyl behave, in some respects, like schizophrenic patients and that this similarity is most striking in the case of thinking processes. In the further investigation of the effects of this drug it was therefore decided to test the hypothesis that Sernyl produces mental disturbances which are characteristic of thought-disordered schizophrenics.

A second, and perhaps more far-reaching, aspect of the current investigation has been concerned with the action of Sernyl upon limiting sensory input. This line of enquiry seemed worth while, not only in terms of the observation made in our previous paper (4) that the drug seemed to alter auditory perception, but also in terms of the apparent link between reduction in type and amount of stimulation on the one hand and mental disturbance on the other.

Material and Methods

Subjects. Both aspects of the investigation were conducted using a sample of normal subjects. This sample comprised 21 individuals ranging in age from 20–50, covering a wide range of occupations. All these subjects were above average in intelligence and none of the subjects were acquainted with the nature of the drugs given nor of the purpose of the experiment.

Subjects were allocated randomly to either the Sernyl (experimental) group or to the Sodium Amytal (control) group, the test administrator being unaware of the drug group to which any individual had been allocated. Ten

subjects formed the Sodium Amytal group and eleven were allocated to the Sernyl group, the additional member of the latter group being necessary because of an error in the administration of the test of thought disorder for one experimental subject. For the auditory threshold test, therefore, the experimental group has an N of 11 while the control group has an N of 10; for the thought-disorder test both groups have an N of 10.

Dosage. All subjects were given the drug, whether Sodium Amytal or Sernyl, prior to the commencement of testing. In each case the drug was contained in an identical capsule. The dosage of Sernyl employed was 7·5 mg., while that of Sodium Amytal was 200 mg.

Methods

1. *Thought Disorder.* It was decided to use the Bannister Test in this connection (1). In his thesis Bannister reported that several of his measures were capable of differentiating between thought-disordered schizophrenics on the one hand, and schizophrenics without thought disorder, normals, neurotics and depressives on the other. Such differentiation was maximized as a measure which he called "Consistency of Relationships" and for this reason only this score was used in our experiment.

For a detailed discussion of the test and its rationale the reader is referred to the original thesis (1), but some idea of the method might be obtained from the following description.

In the test the subject is asked to supply a list of 36 names of people who are known to him, and then is supplied with a list of ten characteristics such as "Good", "Lazy", "Religious", "Prejudiced". He is then asked to take 18 of the names given and divide these into two packs of nine according to each one of the labels—e.g., to divide his 18 names so that the nine "Lazy" people appear in one pile and the remaining nine are left in the other pile. This process is repeated for each of the remaining ideas or constructs.

Next the subject is asked to repeat this procedure, using the same ten constructs, but this time employing the second group of 18 people from the total of 36.

When the subject has completed this second sorting it becomes possible to examine the record of responses in order to see whether certain ideas or constructs go together. If, for example, all the people who are called "Good" by a subject are also called "Religious", then these two ideas would be strongly related for this subject. In general, normal individuals produce *consistent* results for the first 18 and second 18 people supplied by them—i.e., if "Good" and "Religious" are related on the first group of 18, then these two ideas are related on the second group of 18. Thought-disordered schizophrenics on the other hand, tend to show a *lack of consistency* in their usage of constructs and Bannister has employed a simple correlational procedure to indicate the degree of consistency on the two parts of the test.

In the experiment reported here we have compared the consistency of relationship scores for our Sernyl and Amytal groups with the normative data provided by Bannister for thought-disordered schizophrenics (N=8) and normals (N=20) not influenced by drugs.

The experimental procedure involved administration of the drug, either Sernyl or Sodium Amytal, following which the subject was questioned from time to time about his feelings. He was instructed to tell the experimenter as soon as he began to notice any alterations in his physical or psychological state,

but he was not told what drug had been administered, nor was he given any idea as to what experiences might be encountered. When such changes were reported (typically some ¾ hour after taking the drug) the Bannister Test was administered.

2. *Auditory Threshold Changes.* The procedure adopted here was to first test the patient's auditory thresholds on a standard Peter's audiometer before taking the drug, following which re-assessment of threshold took place between the first and second parts of the Bannister Test. The method adopted was to ascertain the threshold on one frequency only (1,000 c.p.s.) by giving ten ascending and ten descending trials, the average of these 20 trials being adopted as the "true" threshold.

The measure of change in audition involved subtracting the average value on the second occasion of testing from that obtained on the pre-drug trials. In the case of Sernyl, our prediction was that the threshold would be lowered after taking the drug, while in the case of Sodium Amytal, as a result of previous work, we predicted a rise in threshold.

Results

1. *Thought Disorder.* Table I shows the results of comparing our two drug groups with Bannister's samples of thought-disordered schizophrenics and normals uninfluenced by drugs. It is clear from these data that our drug samples lie between the other two groups; neither Sernyl nor Sodium Amytal subjects produce scores significantly different from non-drug normals, but while Sernyl subjects are significantly differentiated from thought-disordered schizophrenics the Sodium Amytal subjects are not.

Table I

Significance of differences between Sodium Amytal, Sernyl, non-drug normals and thought-disordered schizophrenics on the measure Consistency of Relationships.

Groups Compared	*t*	Significance Level (1-tail tests)
Sernyl *v.* Sodium Amytal	0·551	N.S.
Sernyl *v.* Non-drug Normals	0·855	N.S.
Sernyl *v.* Thought-disordered Schizophrenics ..	1·804	p=0·05
Sodium Amytal *v.* Non-drug Normals	1·493	N.S.
Sodium Amytal *v.* Thought-disordered Schizophrenics	1·283	N.S.
Non-drug Normals *v.* Thought-disordered Schizophrenics	2·837	p=0·01

These subjects are somewhat equivocal, but they suggest that Sernyl does not, at least in the dosages administered in this experiment, produce effects like those found in thought-disordered schizophrenics. Furthermore, it would appear that on this test of thinking Sernyl has no greater disruptive effects than Sodium Amytal.

2. *Changes in Auditory Threshold.* The statistics in Table II show the results of comparing Sernyl (N=11) and Sodium Amytal (N=10) S's for auditory threshold changes.

TABLE II

Mean change in threshold from pre- to post-drug conditions

Sernyl	Sodium Amytal
—1·106	+0·940

Significance of difference between pre- and post-drug trials

Sernyl	t=1·258 (N.S.)
Sodium Amytal	t=1·498 (N.S.)

Significance of difference between threshold changes for Sernyl and Sodium Amytal groups

t=1·857 (p=0·05)

Although the changes in threshold for the two groups are in the predicted directions, Sernyl lowering and Sodium Amytal raising thresholds, in neither case does the trend achieve an acceptable level of significance. Our first two predictions are, therefore, not confirmed by these data. However, of eleven Sernyl subjects, seven manifest lowered thresholds on the post-drug trials, one remains the same, and two show rises in threshold. Of the ten Sodium Amytal subjects seven show rises in threshold while three manifest the opposite tendency. It would seem that these figures merit further investigation of changes in auditory perception in response to Sernyl.

Our third hypothesis, that the two drug groups would be significantly differentiated respecting their threshold change scores, is confirmed by these data.

DISCUSSION

The disruptive effects of certain drugs can usefully be likened to the action of psychotic processes and Sernyl is one of the most interesting of these chemical compounds. It is clearly necessary to investigate such effects and to examine their similarity to those produced by psychotic illnesses. By this means we may gain some knowledge of the mechanisms involved in psychotic processes.

We have, therefore, adopted an experimental procedure which sets out to answer two problems posed by the action of the drug Sernyl. The first of these problems has been concerned with the effects which Sernyl might have upon thought processes, and in particular whether this drug actually does produce a usage of constructs which appears to be characteristic of patients suffering from "schizophrenic thought disorder". This test which we adopted as a measure of this variable was one devised by Bannister, who was able to show, not only that the test differentiated between thought-disordered schizophrenics and other clinical groups, but between thought-disordered and non-thought-disordered schizophrenics.

The scores achieved by our two drug groups on this test fell somewhere between those obtained by thought-disordered schizophrenics and normals uninfluenced by drugs. While neither drug produced scores significantly different from those obtained by Bannister's normals, only the Sodium Amytal group could not be differentiated from thought-disordered schizophrenics. Our hypothesis that Sernyl produces effects in normals which are similar to those encountered in patients suffering from schizophrenic thought-disorder is therefore negated.

Our second problem has been concerned with beginning to explain some of the clearly disruptive effects of Sernyl by examining one kind of alteration in function produced by the drug. There is a body of evidence which points to a

relationship between certain abnormalities of functioning (such as hallucinations and disturbances in thinking) and reduction in the amount of available stimulation (2, 3, 4, 5, 7) and there is some evidence that certain mental disorders may, in fact, be "normalized" by exposure to such conditions (6).

It seemed to us at least possible that part of the effect of administering Sernyl could be attributed to the consequent alteration in the amount of available sensory input, and in our investigation we have tested one deduction from this thesis. Our prediction has been at this stage only concerned with one direct effect of the action of Sernyl—namely that this drug produces a measurable change in perception in one modality as a result of reducing sensory input in other modalities. Our predictions were not clearly confirmed in this experiment, but the results on the small groups employed certainly merit further investigation. If, on further investigation, we could produce clear-cut evidence for changes in auditory threshold after Sernyl, then it seems possible to set up the hypothesis that a number of the effects of this drug might be accounted for in the same terms, i.e., in terms of reduced sensory input.

One qualifying point should be mentioned. It may be that in the experiments described above, testing was conducted too soon after the administration of the drugs as Sernyl, in particular, produced maximal effects after about $1\frac{1}{2}$ hours, and testing commenced approximately $\frac{3}{4}$ hour after taking the drug. Had we delayed testing until the full effects of the drug had been manifested, larger differences than those actually observed might have been obtained. It could also be argued that larger amounts of drug than those employed in this study might have increased the intensity of the effects and thus maximized the predicted differences. Clearly experiments which make good these faults are necessary and are, in fact, now being undertaken.

Summary

Twenty subjects were given Sodium Amytal or Sernyl and the presence of thought disorder measured by Bannister's Test. The results ran counter to expectation, Sernyl subjects producing scores unlike those found in thought-disordered schizophrenics. In addition changes in auditory threshold were measured. The two drug groups were significantly differentiated by their threshold change scores. These results are discussed and further investigations suggested.

Acknowledgments

We would like to express our gratitude to the volunteers for their co-operation and to Parke, Davis & Co., who provided the Sernyl and supported the investigation.

References

1. Bannister, D., "An Application of Personal Construct Theory to Schizoid Thinking", Unpubl. Ph.D. Thesis, Univ. of London, 1959.
2. Beech, H. R., "Psychological Problems of Solitude and Confinement". Paper delivered at Institute of Biology Symposium on Space Travel". London, 30 September, 1960.
3. Bexton, W. H., Heron, W., and Scott, T. H., "Effects of Decreased Variation in the Sensory Environment", *Canad. J. Psychol.*, 1954, **8**, 70–76.
4. Davies, B. M., and Beech, H. R., "The Effect of 1-Arylcyclohexylamine (Sernyl) on Twelve Normal Volunteers", *J. ment. Sci.*, 1960, **106**, 912–924.
5. Doane, B. K., Mahatoo, W., Heron, W., and Scott, T. H., "Changes in Perceptual Function after Isolation", *Canad. J. Psychol.*, 1959, **13**, 210.
6. Harris, A., "Sensory Deprivation and Schizophrenia", *J. ment. Sci.*, 1959, **105**, 235–237.
7. Lilly, J. C., "Mental Effects of Reduction of Ordinary Levels of Physical Stimuli on Intact Healthy Persons", *Psychiat. Res. Rep.*, 1956, No. 5, 1–9.

CONTROLLED TRIAL OF PROCHLORPERAZINE ("STEMETIL") IN SCHIZOPHRENIA

SOUTH-EAST REGION (SCOTLAND) THERAPEUTIC TRIALS COMMITTEE*

Organization: The late Professor Alexander Kennedy initiated the suggestion that psychiatric drug trials should be on a Regional basis. A Therapeutic Trials Committee was accordingly established under the auspices of the Board of Studies and the Department of Psychological Medicine of the University of Edinburgh, with Professor Kennedy as Chairman. The following clinicians were responsible for the execution of this trial: Dr. G. Bell, Dr. J. K. Morrice, and Dr. R. Ratcliff, at Dingleton Hospital; Dr. A. K. Macrae, Dr. N. Imlah, and Dr. E. Howieson at Bangour Village Hospital; Dr. J. McPherson, Dr. W. W. Gordon, Dr. J. C. Holden and Dr. I. A. Gibson at Gartloch Hospital.

Introduction

Since Delay, Deniker and Harl (1952) first reported favourably on the use of chlorpromazine in disturbed psychotic patients the extended use of phenothiazines has contributed to the transformed atmosphere in mental hospital wards. There is still some doubt as to the precise mechanism of action of the phenothiazines. The blocking of arousal responses to afferent stimulation in animals following chlorpromazine has been fully demonstrated (Bradley and Hance, 1955, 1957). The production in man of a "parkinsonian syndrome" by chlorpromazine and later phenothiazines has been taken as evidence of drug activity as a basal ganglion level (Kruse, 1957). More recent work suggests that chlorpromazine may act by depressing the collateral inflow into the reticular formation from the afferent pathways rather than the brain stem activating system itself (Key and Bradley, 1958).

Clinical experience with the phenothiazines suggests that whereas chlorpromazine has what may be called a "sedative" component in its effect on schizophrenic behaviour the later derivatives seem to have an "activating effect". This is of some importance as the most appropriate treatment of long-stay and often anergic hospitalized schizophrenics is still in dispute. Whereas the phenothiazines have calmed the agitated, overactive and violent patients they have not materially affected the "hard core" of medium and long-stay schizophrenic patients. Many psychiatrists have emphasized approaches other than the pharmacological. Since the time of Conolly at Hanwell it has been recognized that psychological manipulation, including milieu therapy, work therapy and social rehabilitation, can result in significant improvements in behaviour, and to these has been added more recently the application of the principles of dynamic psychotherapy. Nevertheless the overall course of the illness is often not affected.

The efficacy of chlorpromazine in acute schizophrenic illness has been amply confirmed (Vaughan *et al.*, 1957; Kinross-Wright, 1957) and the drug is now often used in place of insulin coma therapy (Boardman *et al.*, 1956).

However, neither chlorpromazine nor some of the other phenothiazine derivatives such as promazine and acetyl promazine have been so effective in the less acute schizophrenic illnesses (Collard and Maggs, 1958). The reports that prochlorperazine was useful in just this group of patients (Milne and Berliner, 1958; Denham, 1958) suggested that the drug merited more extended

* Secretaries: P. G. Fawcett and A. D. Forrest.

trial. Our aim was to assess the value of prochlorperazine in the treatment of chronic schizophrenia and to compare its effect on the illness with that of chlorpromazine.

Material

The patients, all under the age of 60, were selected from three hospitals. One hundred and thirty-two patients were interviewed initially. The interviews were conducted by two psychiatrists working together and using a check list of symptoms to form the symptomatic basis for diagnosis. We took the following definition of schizophrenia given by Fish (1959): "A group of mental disorders in which there is no coarse brain disease and in which many different clinical pictures can occur. The form and content of the symptoms which occur in these different clinical states cannot be understood as arising rationally or emotionally from the affective state, the previous personality or the current situation, with the proviso that where a patient has a severe anxious depression with marked paranoid delusions the illness cannot be considered to be schizophrenia in the absence of clear-cut symptoms of the first rank as defined by Schneider (1955)". Using these criteria ten patients were excluded, some because of signs of organic mental disease. A further ten patients were excluded on administrative grounds, such as the reasonable possibility of the patient leaving hospital before the completion of the trial. Thus 112 patients were left for study. A list of factual data was prepared for each patient and then transferred to "Cope-Chat" punch cards. Using these cards two matching groups (A and B) were prepared. The main factors used in this matching were sex, age, diagnostic subgroup, physique, duration of illness, duration of stay in hospital, presence of delusions, hallucinations, affective disturbance, catatonic symptoms. Taking the 112 patients together there were 54 men and 58 women, the age range was from 20–58 years. Subsequent analysis of the groups A and B showed that the matching had been fairly effective (see Table I).

Table I

Factor	Group A	Group B	Difference
Male	29	25	4
Paranoid	11	13	2
Catatonic and hebephrenic	31	30	1
Other	14	15	1
Duration of illness under 1 year	0	1	1
1–5 years	9	10	1
+5 years	47	45	2
Age under 25	2	2	0
25–40	19	19	0
+40 years	35	35	0
Pyknic	17	18	1
Athletic	8	10	2
Asthenic and dysplastic	31	28	3
Hallucinations	40	43	3
Delusions	40	39	1
Abnormality of thought form	50	51	1
Abnormal affect	50	49	1
Catatonic inhibition	19	19	0
Treated E.C.T.	37	35	2
Hospital under 1 year	7	4	3
Hospital 1–5 years	14	18	4
Hospital +5 years	35	34	1

METHODS

1. *General Description*

We decided that whereas we wished to compare prochlorperazine with chlorpromazine, we also wished to make a comparison with placebo to establish whether the patients under trial did in fact benefit from chlorpromazine. Thus the baseline was chlorpromazine. After initial interviewing and allocation to Groups A and B all patients were placed on chlorpromazine and the dosage was adjusted to produce the maximal behavioural improvement with the minimum side-effects. This dosage adjustment was completed before the onset of the trial proper and determined the dosage throughout the other phases. The format (see Table II) was of the usual double-blind, cross-over variety with the addition of a first month on a stabilized dose of chlorpromazine.

TABLE II

Months	..	..	..	..	..	1	2	3
Group A	..	..	..	..	..	Cl.	X	Y
Group B	..	..	..	..	..	Cl.	Y	X

Cl.=Chlorpromazine. X=Prochlorperazine. Y=Placebo.

2. *Dosage*

As mentioned there was no standard dosage; the dosage was adjusted in the pre-trial period for each patient. In fact the dosage range was from chlorpromazine 25 mg. t.d.s., to 150 mg. t.d.s. This dosage, in terms of the number of 25 mg. chlorpromazine tablets per day, determined the dosage of prochlorperazine and placebo (number of tablets per day). The prochlorperazine tablets contained 6·25 mg. of active substance (dosage ratio of 1 : 4 to chlorpromazine) and, with the placebo tablets, were indistinguishable from the ordinary 25 mg. chlorpromazine tablets.

3. *Methods of Assessment*

(*a*) Weekly rating scales were completed for each patient by the doctor in charge of the ward in conjunction with the nursing staff. These scales were devised by members of the University Department of Psychological Medicine and comprised eighteen different items. Some items were of a simple behavioural type, such as eating, washing habits, level of activity, etc., while others were more specifically psychiatric such as hallucinatory experience, delusions, disturbance of speech form, etc. Each item was rated on a scale from 1 to 5, 1 representing "normal" or no comment and 5 representing "disturbed";

(*b*) Independently of the ward doctors and without discussion with the nursing staff, two members of the University Department interviewed the patients in the pre-trial period and the end of each drug period (i.e. monthly). The interviews were "structured" on the basis of a nine factor symptom scattergram. These factors were entitled hallucinations, delusions, interview attitude, speech form, affect, catatonic inhibition, anxiety, excitement, attention. These headings are evident except perhaps that of affect which was taken here to relate to affective blunting or incongruity of response. Each factor was rated on a three-point scale and on the basis of the completed scattergram a global rating on a five-point scale was made. This scale read in the same direction as that used by the ward doctors, i.e., 1 represented "no comment" and 5 represented "disturbed".

It should be emphasized that all the doctors making these assessments were ignorant of the key to Groups A and B, this information being held by other members of the University Department.

4. *Additional Treatments*

It was decided that any patient who required E.C.T. would have to be withdrawn from the trial. We decided that any additional medication should take the form of Sodium Amytal by day, pentobarbitone or Sodium Amytal at night. Such additional medication was noted on the weekly rating scales completed by the ward doctors. It was also decided that any severe parkinsonism should be treated with benzhexol hydrochloride (Artane).

Results

1. *Withdrawals*

Ten patients were withdrawn during the three-month period of the trial. Three patients became too disturbed. One was started on E.C.T., while the other two were started on specific pharmacological treatment. Three patients were discharged during the course of the trial at the request of their relatives. In two cases the diagnosis had to be revised during the course of the trial. One patient, not previously regarded as an epileptic, developed status epilepticus while the other showed, at successive interviews, emerging evidence of organic intellectual deterioration.

2. *Results*

These are shown in terms of the distribution of each drug group along the axis of the five-point rating scale.

Table III

Drug Group Distribution on 5-Point Rating Scale

	Rating Scale Positions					
Drug periods	1	2	3	4	5	Totals
Chlorpromazine	7	29	35	25	6	102
Prochlorperazine	14	13	39	29	7	102
Placebo	14	16	38	28	6	102
Totals	35	58	112	82	19	306

$p = <0{\cdot}3 > 0{\cdot}2$ if $n = 8$.

Table IV shows the same results expressed in the conventional terms; improved, unchanged and worse. These differences are not significant ($p = <0{\cdot}1 > 0{\cdot}05$ if $n = 2$).

Table IV

	Improved	Unchanged	Worse	Totals
Prochlorperazine	24	47	31	102
Placebo	27	48	27	102
Totals	51	95	58	204

As noted under methods the dosage for each patient was determined in the pre-trial phase on the basis of clinical response. We decided that it might be

of interest to analyse the results of prochlorperazine in accordance with dosage, the threshold being set at 75 mg. daily (see Table V).

TABLE V

Results of Treatment in Relation to Dosage

	Improved	Unchanged	Worse	Totals
Prochlorperazine— less than 75 mg. per day	15	28	19	62
Prochlorperazine— 75 mg. per day or more	9	19	12	40
Totals	24	47	31	102

We had wondered whether amongst those patients receiving the higher doses of prochlorperazine the greatest number of deteriorations might not occur, owing to the distorting effects of unrecognized parkinsonism. In fact the percentage incidences of deterioration, 30·0 per cent. for the higher dosage and 30·6 per cent. for the lower dosage are not significantly different. Similarly the percentage improvements, 22·2 per cent. at the higher and 24·2 per cent. at the lower dosage, are not significantly different.

Next we considered whether the different order of drugs in Groups A and B might not affect the outcome. In Group A the order was chlorpromazine—prochlorperazine—placebo, while in Group B it was chlorpromazine—placebo —prochlorperazine.

TABLE VI

Results in Relation to Order of Drug Administration

		Improved	Unchanged	Worse	Totals
Group A	Prochlorperazine ..	10	22	19	51
	Placebo	15	22	14	51
Group B	Prochlorperazine ..	14	25	12	51
	Placebo	12	26	13	51
	Totals	51	95	58	204

The percentage deterioration for Group A and Group B on prochlorperazine, 37·3 per cent. and 23·5 per cent. respectively, are notably, though not significantly, different ($p = <0·3 > 0·2$).

The next table shows the results of treatment with prochlorperazine and placebo in relation to diagnostic group but irrespective of drug order.

TABLE VII

Results of Treatment in Relation to Diagnostic Groups

		Improved	Unchanged	Worse	Totals
Prochlorperazine	Paranoids ..	9	5	6	20
	Others ..	15	42	25	82
Placebo	Paranoids ..	7	9	4	20
	Others ..	20	39	23	82
Totals		51	95	58	204

It is clear from Table VII that the treatment results are not closely linked with any diagnostic grouping.

In the next table (Table VIII) we have investigated the groups of patients who improved with prochlorperazine and with placebo in an attempt to elucidate what factors differentiated them from the patients who did not improve. The analysis suggests, in fact, that the patients who improved could not be differentiated on any of the factors studied from the trial group as a whole.

TABLE VIII

Analysis by Factors of Patients Improved on Prochlorperazine (24), Improved by Placebo (27), and the Entire Trial Group (112)

Factor	Placebo Improved (27 Patients)	Prochlorperazine Improved (24 Patients)	Total Trial Group (112 Patients)
Male	14 (51·8%)	14 (58·3%)	54 (48·2%)
Age under 40 years ..	15 (55·1%)	12 (50%)	42 (37·5%)
Paranoids	6 (22·2%)	7 (29·4%)	24 (21·4%)
Illness under 5 years ..	6 (22·2%)	5 (20·8%)	20 (17·9%)
Pyknic build	7 (25·9%)	7 (29·4%)	35 (31·2%)
Hostility	6 (22·2%)	4 (16·7%)	25 (22·4%)
Hallucinations	15 (55·1%)	17 (70·8%)	83 (74·1%)
Excitement	5 (18·5%)	4 (16·7%)	22 (19·7%)
Hospital under 5 years ..	10 (37·1%)	9 (37·5%)	44 (39·4%)

So far all the tables have been based on the five-point rating scale completed by the two psychiatrists and using the symptom scattergram. Analysis of the Behaviour Rating Scale used by the doctors in the three hospitals revealed a similar absence of significant shift in group distribution during the three drug periods. The data for Factor 9 (hallucinations) and Factor 10 (delusions) are shown in Tables IX and X.

TABLE IX

Behaviour Rating Scale: Factor 9 (Hallucinations) Group Distributions During Three Drug Periods. Rating Scale Positions

		1	2	3	4	5	Totals
Drug Periods	Chlorpromazine	55	25	13	7	2	102
	Prochlorperazine	57	22	12	7	4	102
	Placebo	64	14	14	8	2	102
	Totals	176	61	39	22	8	306

$p = <0·8 > 0·7$ if n=8.

TABLE X

Behavioural Rating Scale: Factor 10 (Delusions). Group Distribution Along 5-Point Rating Scale During Various Drug Periods

	5-Point Rating Scale					
Drug periods	1	2	3	4	5	Totals
Chlorpromazine	72	5	17	8	0	102
Prochlorperazine	67	4	25	6	0	102
Placebo	69	5	20	7	1	102
Totals	208	14	62	21	1	306

$p = <0·9 < 0·8$ if n=8.

Discussion

Briefly our results indicate that of patients stabilized on chlorpromazine and then transferred to prochlorperazine less than one-quarter improved (23·5 per cent.) whereas 46·1 per cent. remained unchanged and 30·4 per cent. became worse. Our results do not, therefore, support the suggestion that prochlorperazine is going to prove of particular value in the hospitalized schizophrenic. Analysis of the group of 24 patients who did improve on prochlorperazine demonstrates that this group did not deviate significantly from the trial group as a whole. Nevertheless it may be significant that amongst those improving on prochlorperazine there were a disproportionate number of paranoid patients. It is well recognized that this group carries in any case a more favourable prognosis and does well with other neuroleptic drugs (McDonald and Watts, 1959). The interesting observation that comes out of this trial is that more than a quarter (26·5 per cent.) improved when transferred to placebo.

These results might be thought to cast doubts on the methods of assessment used. To check the reliability of the rating scale based on the structured interview we analysed the rating distribution for Groups A and B at the end of the first month. At this point all the patients had been on chlorpromazine for one month. As we know the degree of matching between the groups we postulated that calculation of the correlation co-efficient between the rating distribution for Groups A and B would give us an index of the reliability of the scale. The calculation shows that $r=0·729$ with a p value of $<0·17$.

In the same way we analysed the rating distributions for Groups A and B on the Behaviour Rating Scale for Factors 2 (under-activity) and 8 (disorder of speech function) at the end of the first month. Calculations of the correlation co-efficients give, for Factor 2, $r=0·96$ and $p<0·025$ while for Factor 8 $r=0·99$ and $p<0·005$. The much higher reliability of the Behaviour Rating Scales as compared with the global scale based on the structured interview is to some extent offset by the fact that the group distributions on the Behaviour Rating Scales show a bias to the left or normal end of the scale (see Table XI).

Table XI

Distribution on Behaviour Rating Scale of Groups A and B at the End of the Fourth Week (Factor 2 = Under-activity, Factor 8 = Disordered Speech Function)

		Rating Positions					
		1	2	3	4	5	Totals
Factor 2	A	18	24	4	5	0	51
	B	16	28	7	0	0	51
Factor 8	A	30	8	9	4	0	51
	B	32	5	8	5	1	51
Totals		96	65	28	14	1	204

Turning now to the literature on prochlorperazine it is conspicuous how few of the investigations reporting positive results employed adequate controls. Thus Riesenman and Pettit (1959), Denham (1958) and Galbraith *et al.* (1959) all reported good results with prochlorperazine. None employed satisfactory

controls. Goldman (1958) reported 27·5 per cent. complete recovery from all active psychotic symptoms out of a total of 320 schizophrenic patients treated and Frierson (1958) noted 60 per cent. improvement out of a total of 33 "chronic psychotic patients". Neither of these two authors used controls. Foulds (1958) has an interesting table analysing 72 papers reporting on the results of psychiatric treatment. Fifty-two projects had no controls and 43 gave positive results. Twenty projects used controls and only 5 gave positive results. Applying the usual tests of probability to these figures Foulds showed that this distribution could not have occurred by chance ($p < \cdot 001$). In other words uncontrolled drug trials in psychiatry tend to give positive results.

One of the better controlled studies on prochlorperazine in psychosis is that of King and Weinberger (1959). They compared three groups of schizophrenic patients over a period of ten weeks. One group received a lactose, one group received chlorpromazine and the third received prochlorperazine tablets. All three groups showed a significant improvement though this was greatest for those receiving chlorpromazine. The authors suggest, on the basis of their observations, that the therapeutic effects of the phenothiazines are not closely linked with their effect of producing parkinsonism. In our study only four patients developed parkinsonian rigidity (one of these also showed tremor and salivation). None of these patients showed any improvement in mental state or behaviour while receiving prochlorperazine. The parkinsonism was well controlled with benzhexol hydrochloride.

Neither did we encounter any significant side-effects (cf. Sainsbury, 1959). One patient experienced a mild cerebro-vascular incident while on prochlorperazine. He was taken off the drug and the symptoms of hemiparesis cleared up over a period of a week.

There are a few points concerning methodology which have emerged during this trial. Firstly, while we think that the Behaviour Rating Scale we employed is fairly reliable, yet the data on the 18 factors is very difficult to process. Each factor has to be analysed separately and the work involved in this analysis is not commensurate with the information derived. We are planning to construct a much simpler scale comprising five factors on a five-point scale.

Secondly the cross-over type of trial is subject to criticism. In this case the trial itself lasted three months to which must be added two weeks for preliminary study, so that the collection of sufficient suitable patients who are likely to remain in hospital for that period becomes a problem. In this trial the difficulty was minimized by the fact that three different hospitals were involved. Another factor to be noted is that the longer the trial continues the greater the chance of spontaneous fluctuation in the patient's condition. Nevertheless it is clear that in assessing the effect of phenothiazines in schizophrenia it is necessary to exhibit the drug for several weeks; nor can the trial be shortened by the omission of controls.

Finally, our results suggest that a certain proportion of hospitalized schizophrenics do not require drugs at all. While this may be self-evident to older and more experienced psychiatrists, it does seem that this point is not always recognized by younger staff members, and, if these expensive and in some cases potentially toxic drugs are to be used liberally on chronic schizophrenics, one would wish to see their value proved fairly conclusively. It seems justifiable here to quote Houston (1956) discussing the results of a controlled trial in schizophrenia; "The main lessons that emerge from the study are that caution and adequate control procedures are essential before any therapy or drug is accepted as beneficial in chronic psychotics . . ."

Summary

1. A controlled trial of prochlorperazine on chronic schizophrenic patients has been described.

2. The behavioural changes obtained did not differ significantly from those produced by placebo or chlorpromazine.

3. The methodology of the trial and the implications of the results have been discussed.

References

Bradley, P. B., and Hance, A. J., 1957.
Iidem, 1957, *EEG Clin. Neurophysiol.*, 1957, **9,** 191.
Boardman, R. H., Lomas, J., and Markowe, M., *Lancet*, 1956, *ii*, 487.
Collard, J. F., and Maggs, R., *Brit. Med. J.*, 1958, **1,** 1452.
Delay, J., Deniker, P., and Harl, J. M., *Ann. Med. Psychol.*, 1952, **110,** 112.
Denham, J., *J. Ment. Sci.*, 1958, **104,** 1190.
Fish, F. J., *Geron. Clin.*, 1959, **1,** 127.
Foulds, G. A., *J. Ment. Sci.*, 1958, **104,** 259.
Frierson, B. D., *J. Nerv. Ment. Dis.*, 1958, **126,** 585.
Galbraith, A. J., Hewat, J. K., and MacNamara, D., *J. Ment. Sci.*, 1959, **105,** 256.
Goldman, D., *Amer. J. Med. Sci.*, 1958, **235,** 67.
Houston, F., *Brit. Med. J.*, 1956, *i*, 949.
Key, B. J., and Bradley, P. B., *Nature*, 1958, **182,** 1517.
Kinross-Wright, V., *Med. Clin. N. Amer.*, 1957, **41,** 295.
King, P. D., and Weinberger, W., *Amer. J. Psychiat.*, 1959, **115,** 1026.
Kruse, W., *Dis. Nerv. Syst.*, 1957, **18,** 1.
Macdonald, R., and Shields Watts, T. P., *Brit. Med. J.*, 1959, *i*, 549.
Milne, R. B., and Berliner, F., *J. Ment. Sci.*, 1958, **104,** 873.
Riesenman, F. R., and Pettit, M. B., *Amer. J. Psychiat.*, 1959, **115,** 1032.
Sainsbury, P., and Lucas, C. J., *Brit. Med. J.*, 1959, *ii*, 737.
Schneider, K., *Klinische Psychopathologie*, 1955. Stuttgart.
Vaughan, G. F., Leiberman, D. M., and Cook, L. C., *Lancet*, 1955, *i*, 1083.

EXPERIENCE WITH THIORIDAZINE ("MELLERIL") THERAPY

By

N. GOLD, M.B., B.S., D.P.M.

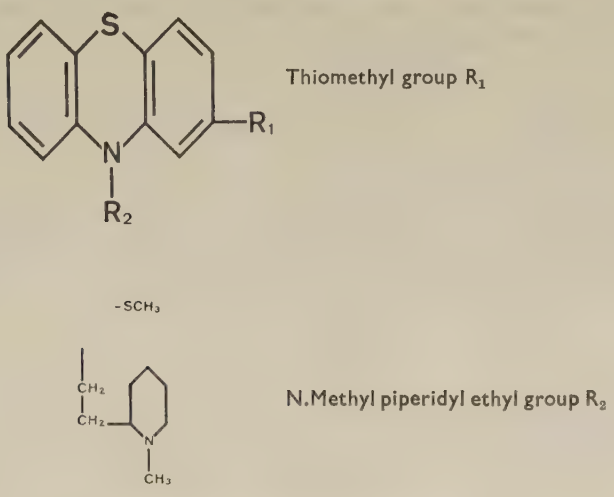
Senior Registrar

Park Prewett Hospital, Basingstoke

"A doctor must know not only the virtue of a drug, but also its drawbacks"—
Carling (1960).

THIORIDAZINE is one of the newer phenothiazine derivatives used in psychiatry. Previous workers have reported few serious side-effects with it. The following pilot trial was carried out on male patients suffering from chronic schizophrenia who required nursing in a closed ward.

PHARMACOLOGY



Phenothiazine basic structure

Thioridazine possesses the basic phenothiazine structure with a thiomethyl group at position 2 and a N.Methyl piperidyl ethyl group at position 10 (see figure). It is claimed that substitution of a N.Methyl piperidyl ethyl group at the 10 position abolishes most of the adrenolytic and anticholinergic activity of the drug.

Thioridazine has little anti-emetic effect, is less effective in producing hypothermia and is not so powerful a sedative, comparing these effects with

other phenothiazines, particularly chlorpromazine. Taeschler and Cerletti (1959) having done considerable work on the pharmacology of thioridazine suggest that the absence of extra-pyramidal side-effects is related to the difficulty in producing catalepsy in experimental animals.

Selection of Patients

Thioridazine has been used both in psychotic and neurotic disorders and has been recommended for hyperkinetic, violent, agitated, anxious and assaultive patients. Smith *et al.* (1959) used thioridazine with success on patients who were refractory to previous therapy. In view of this it was decided to carry out a trial on schizophrenic patients who were in the only locked male ward.

As thioridazine was only available in tablet form, patients who were likely to be reasonably co-operative (and take the tablets) were selected and because of this only 23 were suitable.

Age distribution	21–30	31–40	41–50	51–60
	2	9	8	4

Their duration of hospitalization ranged from 2 to 22 years.

Medication at the time of trial included promazine, perphenazine, chlorpromazine, trifluopromazine, promethazine, paraldehyde, barbiturates and lithium citrate. All the patients were regarded as having failed to have benefited from these treatments. Six patients had been leucotomized during the period 1949–54. Electroplexy had been given in the past.

Ward structure does not include a protective room.

The entertainment provided includes a weekly cinema show and a weekly dance in the main hall; in the ward TV, radio, billiards, snooker and table skittles are available and weekly "closed ward" socials which entail visits to or from the corresponding female ward.

The patients perform domestic work in the ward, O.T. work is carried out in the ward and O.T. centre. Some patients work on the hospital farm.

All these factors were constant during the trial.

Drug Dosage

Following Sandison (1960) it was begun at 50 mg. t.d.s. It was increased gradually until most of the patients were on 400 mg. a day. Three were further increased to 600 mg. a day in divided doses after four weeks.

Assessment of the Patients

Behaviour Rating

A rating scale, modified from Baker and Thorpe (1956) was used to measure deterioration and restlessness to see if the drug therapy improved the patients.

Rating was done by the multiple observer method using the charge nurses and staff nurses who knew the patients very well. They were continually on the alert for any alteration in the patient. The 23 patients were divided into one group of 11 and another of 12 so that the smaller groups enabled the direct

observation method to be more accurate. Each charge nurse and staff nurse on both shifts observed different groups from 7 a.m. until 10 p.m., thus obtaining four independent ratings for each patient over a two-day observation period. (Stencilled scales were filled in independently and each observer put his results into an envelope which was sealed and handed in at the end of the shift.) The night staff recorded detailed observations on the patients from 10 p.m. to 7 a.m.

RATING SCALE

	4	3	2	1	0
A	Motionless.	Occasional movement.	Very retarded.	Slightly retarded.	Normal.
B	Wildly excited —needs isolation all day.	Needed isolation for a short period.	Restless all day.	Restless for a short period.	
C	Tube fed.	Spoon fed.	Eats only with persuasion.	Finicky with food.	
D	Mute.	Occasional word with persuasion.	Speaks only if spoken to.	Occasional spontaneous remark.	
E	Needs dressing fully.	Needs help in dressing.	Dresses self but needs adjustment.	Dresses self but untidy.	
F	Does no work.	Works with supervision in ward.	Works with supervision outside ward.	Works without supervision	
G	Doubly incontinent several times.	Doubly incontinent once.	Incontinent of urine several times.	Incontinent of urine once.	
H	Aggressive several times without provocation.	Aggressive once without provocation.	Aggressive several times when approached.	Aggressive once when approached.	
I	Has no friends.	Friendly towards one of staff.	Friendly towards one patient.	Friendly towards two people.	
J	No interest in entertainment.	Rarely interested in entertainment.	Occasional interest in entertainment.	Frequent interest in entertainment.	
K	Always hallucinated and/or deluded.	Frequently hallucinated.	Sometimes hallucinated.	?Hallucinations.	

A 5-point Rating Scale with 0 Equal to a Normal Response and 4 the Most Abnormal Response

Daily assessments on each patient were performed for a week while they were on their previous medication.

After this all drugs were stopped and the daily assessments continued for a period of three days. Thioridazine was then commenced and assessments were continued twice weekly for thirteen weeks. While on maximum dosage the thioridazine was suddenly stopped and the ratings were continued for a further four weeks.

Standardized Interviews

These were also carried out at the beginning of the trial and eight weeks later by the investigator. Each patient was interviewed separately in the ward clinic and a number of questions which were unlikely to produce an emotional reaction in the patient were asked and the responses noted.

Laboratory Investigations

Using the method of Leach and Crimmin (1956) regular examination of the urine was done to determine if the patients were absorbing thioridazine. Total white blood counts and differential counts were performed at six weeks and twelve weeks.

Results

One aggressive patient who had required regular paraldehyde medication, mean daily dose 4·5 drachms (range 4–8), was controlled while on thioridazine on a lower dose, mean 1 drachm, for some days no paraldehyde was given. No windows were broken during the trial nor were there any attempts to escape by the 23 patients. Night reports were generally of peaceful nights, the exceptions were due to patients not on thioridazine therapy.

Hollister and McDonald (1959) found weight changes in their patients while on thioridazine and during the trial these were noted as follows: 16 patients gained weight by 2 to 18 pounds, mean 8 pounds, most of these were in the younger age group. Six patients lost weight, 2 to 8 pounds, mean 3 pounds, most of these were in the older age groups. The weight of one patient was unchanged. Of the patients who had undergone leucotomy, three gained and three lost weight.

Repeated blood counts showed mostly normal total white cells, 7 had a relative lymphocytosis. Three had a slight leucocytosis, up to 13,000 c.mm. on one occasion. Leucopenia was not found. Urine analysis proved that thioridazine was being absorbed by all patients.

Ophthalmoscopy did not reveal retinal changes, the dosage was considerably below that used by May *et al.* (1960) who have reported retinal pigmentation and oedema.

It had been thought that toxicity to the retina could be prevented by the use of a sulphur-containing radical replacing a halogen at position 2 on the phenothiazine nucleus.

No extrapyramidal involvement or jaundice was seen. Photosensitivity did not occur in spite of frequent and prolonged exposure to strong sunlight while on 400 and 600 mg. a day, this contrasts with the report by Kent (1960).

There were no subjective complaints of a dry mouth or nasal stuffiness. When staff supervised the tablets being swallowed they noticed that the mouths were generally moist.

The standard interview did not reveal any significant change in the patients.

The rating scores gave a high measure of agreement by the observers.

Assessing the results of Behaviour Rating showed 6 patients unchanged, 2 more were retarded without any benefit and 15 made an improvement on their initial ratings by one point. Of these 15, 6 became more retarded but showed other improvement. Seven patients improved in more than one characteristic (see Table).

TABLE

Results of Changes in Behaviour Rating

Patient 1	.. ..	A	0–1	Patient 10	.. ..	A	0–1
						B	2–1
						C	1–0
2	.. ..	A	0–1			E	1–0
						F	4–3
						H	1–0
3	.. ..	F	4–3			I	2–1
						J	3–2
4	.. ..	A	1–2	11	.. ..	A	0–1
		D	2–1			B	1–0
						F	3–2
						J	2–1
5	.. ..	D	3–2				
		F	3–2	12	.. ..	A	1–2
						F	3–2
						H	1–0
6	.. ..	D	2–1			J	3–2
7	.. ..	D	3–2	13	.. ..	A	0–1
		J	3–2			B	1–0
8	.. ..	A	0–1	14	.. ..	I	2–1
		F	3–2				
		J	2–1				
				15	.. ..	F	3–2
9	.. ..	E	2–1	16	.. ..	I	2–1
		F	3–2				
				17	.. ..	F	3–2

A	B	C	D	E	F	H	I	J
8	3	1	3	2	9	2	3	5

While the improvement in working ability agreed with the findings of Haug (1959) the retardation noted is contrary to his findings.

WITHDRAWAL EFFECTS

During the four-week period after the drug was stopped, 11 patients who had improved became disturbed and were recommenced on thioridazine. One patient who had not shown any improvement while on the drug was worse without it and was improved when treatment recommenced. Five who had improved maintained their improvement for four weeks after cessation of drugs.

One patient during the first three days had 2 withdrawal fits, having previously been on barbiturate therapy.

Asymptomatic hypotension was detected in one patient—his records revealed that he had been hypotensive two years before; no cause was found for this.

DISCUSSION

No blind trial was used because of the numerous objections to the placebo response (it has been commented that the investigator is the only one who

does not know when the active or inert substance is being used in a drug trial).

Instead all the patients who were accustomed to the ward and had been on numerous therapies prior to this trial received thioridazine, which was just another white tablet to them. In this way they were used as their own controls and were assessed before, during and after the cessation of thioridazine therapy.

Multiple observers were used to minimize observer bias. Although it is not possible to prevent contamination due to the observers hoping for improvement, they were frequently reminded that only the side-effects were being sought. The drug was not boosted as a panacea.

The continued improvement of the five patients off treatment might be due to altered habits during the course of the trial.

A recent review by Hurst (1960) of phenothiazine derivatives which are in current use in psychiatry does not deal with thioridazine. It gives as the three most serious side-effects parkinsonism, jaundice and agranulocytosis.

The parkinsonian syndrome may be associated with chlorpromazine, perphenazine, fluopromazine, trifluoperazine and prochlorperazine. Jaundice may occur with chlorpromazine, pecazine and acepromazine. Chlorpromazine, promazine, pecazine, trimeprazine and methotrimeprazine may cause agranulocytosis.

From the present trial the absence of any serious side-effect agrees with the findings of Sandison *et al.* (1960). It appears that thioridazine used in doses similar to chlorpromazine is a safe and effective phenothiazine derivative.

Summary

Twenty-three male chronic schizophrenics in a closed ward were treated with thioridazine for 13 weeks. No side-effects were noticed except for slight drowsiness. Two patients were worse and 6 were unchanged; 15 improved.

Alterations in weight occurred but were not related to the clinical picture.

Thioridazine produced drowsiness as its only side-effect in daily doses of 400 to 600 mg.

When the drug was stopped, 11 became worse and were put back on thioridazine.

Acknowledgments

My thanks are due to Dr. I. Atkin and Dr. E. C. Turton for permission to carry out this trial and the nursing staff of M.6 for their willing co-operation. Sandoz Products Ltd. generously supplied thioridazine tablets.

References

Baker, A. A., and Thorpe, J. C., *J. Ment. Sci.*, 1956, **112**, 840.
Carling, E. R., *The Medico-Legal Journal.* Vol. XXVIII, Part II, p. 65.
Haug, J. O., *Tidsskrift for den Norske Laegeforening*, 1959. **79**, (6), 317.
Hollister, L. E., and McDonald, B. F., Communication at California Medical Association. February, 1959.
Kent, D. A., *Brit. Med. J.*, 1960, 5189. 1–1888.
Leach, H., and Crimmin, W. R. C., *J. Clin. Path.*, 1956, **9**, 164.
May, R. H., Selymes, P., Weekley, R. D., and Potts, A. M., *J. Nerv. Ment. Dis.*, 1960, **130**, 230.
Sandison, R. A., Personal communication, 1960.
Idem, Whitelaw, E., and Currie, J. D. C., *J. Ment. Sci.*, 1960, **106**, 732.
Smith, J. A., Christian, D., Rutherford, A., and Henderson, H. C., Scientific Exhibit. American Psychiatric Association. P.A. April 27.
Taeschler, M., and Cerletti, A., *Nature*, 1959, **811**, 823.
Hurst, L., *J. Ment. Sci.*, 1960, **106**, 443, 755.

AN EVALUATION OF THE DOUBLE-BLIND TRIAL AS A METHOD OF ASSESSING PROMAZINE ("SPARINE") IN THE TREATMENT OF CHRONIC PSYCHOTIC PATIENTS

By

M. A. HARGREAVES, M.B., B.S., D.P.M.*

Warley Hospital, Essex

Most people now accept the value of the tranquillizer or ataractic drugs, which play a major role in individual therapeutic results and in environmental change in major psychiatric hospitals. Numerous surveys have stressed the influence of these drugs and they have recently been confirmed by Brill and Patton (1959) in a twelve-year review of mental hospitals capable of dealing with over ninety-three thousand patients. As the number of patients on tranquillizing drugs (mainly chlorpromazine) increased, so the patients requiring restraint decreased, the discharges increased and the re-admissions decreased: a direct cause and effect relationship was established.

Few workers dealing with chronic psychiatric patients would like to return to the conditions before the introduction of the tranquillizers, and it may well become as unlikely for a medical student to see a chronic psychotic not under phenothiazine therapy as it is now for him to see a lobar pneumonia run its classical course.

Unfortunately chlorpromazine, which was the first of the phenothiazine tranquillizers and is probably still the most widely used, has a number of side-effects which may not only affect the patients but also the nursing staff. In this hospital a number of nurses developed proven skin sensitivity to chlorpromazine and it was decided to second them to a ward where this drug would not be used. The population of this ward were female chronic schizophrenics who were therefore denied treatment with chlorpromazine and were thus a virgin field for assessing other phenothiazines, as long as cross-sensitivity with chlorpromazine did not exist. This situation seemed to be ideal for conducting a clinical trial, as it would give a much more realistic picture of a drug's action than the trials commonly conducted nowadays where new drugs are given to groups of patients who have proved resistant to previous regimes with similar drugs.

When promazine ("Sparine") was introduced, preliminary trials demonstrated that nurses could handle the drug without recurrence of their chlorpromazine-induced skin sensitivity. Similar findings have been reported by Mitchell (1956), Fox (1956) and Morgan and Van Leent (1958). Patients have also been able to tolerate promazine although allergic manifestations occurred with chlorpromazine (Graffagnino *et al.*, 1956; Usdin, 1956). Cross-sensitivity is therefore not an important feature between these two phenothiazines, although occasional cases of allergic reactions to promazine have been observed (Azima and Durost, 1957; Ayd, 1957). It has been suggested

* Present address: United Birmingham Hospitals, Queen Elizabeth Hospital, Birmingham.

by Goodman and Cahn (1959) that the chlorine atom on the phenothiazine nucleus accounts for the skin reactions produced by chlorpromazine and drugs with a similar structure.

As promazine appeared to be acceptable to the skin-sensitive nursing staff and as conflicting results had been reported on its use in chronic psychotics, it was decided to conduct a pilot trial as a possible preliminary to a larger double-blind study.

Pilot Trial

Six of the most aggressive, and unco-operative patients who sadly neglected their personal hygiene and needed constant supervision and attention were selected for the pilot trial. The average age was 62 years and the average length of time in hospital was 31 years.

All were given promazine in the form of a concentrated solution which had been made into a pleasant elixir by the hospital pharmacist. Treatment was started at a dosage level of 300 mg. promazine daily and was increased slowly until beneficial or toxic effects appeared.

In all cases promazine was eventually given at 900 mg. daily and continued at that level for two to three months. No toxic effects were observed at this dosage level and the results were dramatic. Four out of the six patients improved sufficiently to be able to help with ward work, all lost their aggressiveness and destructiveness and became very much more co-operative so that they were easier to manage with minimum supervision. It was noticeable, however, that optimum results were not usually apparent until after six weeks' therapy.

This pilot trial was, of course, uncontrolled, but the results were sufficiently encouraging to proceed with a fully controlled double-blind trial using the dosages which had been found effective but safe.

Method

The ward to which the chlorpromazine-sensitive nurses were seconded and which was used for this trial accommodated sixty-four female patients of whom fifty were selected. All were chronic schizophrenics and had been in hospital for periods ranging from 2 to 41 years, the average duration of stay being 24 years. Ages varied from 30–70 years, with an average of 56 years. Of this population, forty-three completed the six months' trial, two were withdrawn because of side-effects and five for reasons beyond our control.

The medication used was promazine in solution at a concentration of 50 mg. per ml. and an inert solution with similar properties as far as taste and appearance were concerned. Both were formulated into palatable flavoured elixirs by the hospital pharmacist, who also held the key of the double-blind trial in an attempt to eliminate bias from the observations of the medical and nursing staff.

The trial was conducted over a six-months' period with each patient receiving promazine for three months and the identical placebo preparation for the other three months. Half of the patients started with promazine and half with placebo; the selection was made according to random tables.

In order to make the trial as realistic as possible and to mimic conditions of treatment in normal circumstances a variation in dosage was allowed in the design. Dosage started at 300 mg. daily in three divided doses and was increased within nine days to 900 mg. daily if permitted by the condition of the patient. Similarly the dose could be reduced if side-effects occurred. It was felt

that this device would reduce the shortcomings of the fixed-dose clinical trial which so often bears no relationship to the normal usage of drugs in clinical practice.

Assessments were made on charts as shown below (Fig. 1) with the senior nursing staff reviewing the patients daily and recording their findings weekly, as follows:

Much worse	0
Worse	1
No change	2
Good	3
Very good	4

The total scores for each patient on each assessment were then made omitting the first four weeks of each treatment because of the delay in effect mentioned earlier.

Results

During both halves of the trial a proportion of the patients receiving the active preparation could be distinguished from those on the placebo but this was more marked in the first three months when there was no continuing effect of the promazine during the placebo period.

It was noticeable that this difference between patients on active and patients on inert medication could only be made when the maximum dosage had been reached and when the drugs had been given for about six weeks. It was therefore confirmed early in the trial that there was a latent period before the drug's action was exerted, as had been shown earlier in the pilot study.

These observations may have interfered with the "blindness" of the double-blind trial but this is to some extent unavoidable with any potent treatment and really makes the use of the double-blind technique unnecessary for the evaluation of the drug.

In general about half of the original fifty patients improved on promazine and made sufficient progress to justify continuation of the drug. Apart from the specific factors listed in Figure 1, the overall improvement made the patients more manageable and accessible. This was particularly apparent from a nursing point of view and was illustrated by the ability of 28 of the patients to go on a day's outing organized by the hospital. The majority of these patients were schizophrenics of about 30 years standing and any similar outing could not possibly have been undertaken in the past. Despite this, the sister who accompanied them reported that they were all neatly dressed, behaved themselves extremely well and showed no signs of their previous degraded habits.

This improvement in so many patients made a great alteration in the ward generally so that untreated patients indirectly derived benefit.

Just as beneficial effects did not show themselves for four to six weeks on promazine, so these improvements continued for many weeks after the withdrawal of the active drug.

In addition to the day-to-day observations made on the patients which were recorded by the nursing staff, who put a cross on the chart in the appropriate square, a final assessment was made by the charge nurse of the condition and progress of the patient.

FIGURE 1

Name: ..... Age: ..... No. in Trial: .....

Ward: ..... Hospital No. .....

Clinical Condition: .....

(Please put a cross in the approp. square in each section.)	General Aggressive Behaviour					Over-Activity					Noisiness					Self-care					Drugs other than Susp. needed to control the patient
Date	Very bad	Bad	Average	Good	Very good	Very bad	Bad	Average	Good	Very good	Very bad	Bad	Average	Good	Very good	Very bad	Bad	Average	Good	Very good	
Initial Observations																					
	Much worse	Worse	No change	Better	Much better	Much worse	Worse	No change	Better	Much better	Much worse	Worse	No change	Better	Much better	Much worse	Worse	No change	Better	Much better	

Reverse of Proforma

DEFINITION OF TERMS:

General Aggressive Behaviour:

Very bad: Consistently aggressive, and impulsive towards other patients. Spiteful and resistive to nursing staff.

Bad: Aggressive and evasive most of the time, resisting efforts of nursing staff.

Average: Resenting interference and occasionally aggressive.

Good: Co-operative most of the time but occasionally resistant to supervision.

Very good: Never resistant or aggressive with co-operation practically all the time.

Over-Activity:

Very bad: Always destructive, tearing clothes and papers. Filling pockets with all sorts of rubbish. Talking and laughing to themselves. Requiring toilet supervision.

Bad: Frequently doing above.

Average: Sometimes shows useless activity.

Good: Quiet for most of the day with occasional bouts of over-activity.

Very good: Practically always quiet.

Noisiness: Self-explanatory.

Self-Care:

Very bad: Requiring all nursing attention, including washing, dressing and hand feeding. Is also doubly incontinent.

Bad: Remedies grosser defects such as spilt food on clothing, but no other efforts at self-care.

Average: On the whole uninterested in clothes or appearance, but fairly clean.

Good: Improves appearance with cosmetics, but will not wash or change clothing.

Very good: Takes fairly good care over personal appearance.

The total scores of the patients over the six-month period of the trial from the day-to-day assessments are given below, in Table I.

TABLE I

I. Sparine Given for First Three Months and Placebo for Latter Three Months

Case Number	General Aggressive Behaviour		Over-Activity		Noisiness		Self-Care	
	Sparine	Placebo	Sparine	Placebo	Sparine	Placebo	Sparine	Placebo
1 ..	11	23	11	23	24	24	8	18
2 ..	26	32	26	29	18	32	17	32
3 ..	16	16	16	16	16	24	26	24
5 ..	18	2	23	8	23	32	23	18
6 ..	16	31	20	31	20	31	17	31
8 ..	32	32	32	32	32	32	28	32
9 ..	14	31	14	25	14	31	21	31
12 ..	16	16	24	24	24	24	24	24
15 ..	22	32	22	32	20	18	22	32
18 ..	23	32	30	32	30	32	30	32
19 ..	21	Nil	22	16	22	8	22	24
21 ..	23	32	23	32	19	32	14	16
24 ..	32	8	32	13	32	32	32	32
25 ..	2	Nil	1	Nil	4	Nil	5	Nil
30 ..	32	32	32	32	32	32	32	32
34 ..	26	32	26	32	27	31	32	32
35 ..	28	32	28	32	28	32	28	32
37 ..	12	Nil	12	Nil	14	7	13	Nil
40 ..	32	11	32	25	32	32	32	24
46 ..	17	16	16	16	16	16	16	13
48 ..	Nil	16	16	16	Nil	16	16	16
50 ..	29	24	31	24	25	24	24	24
Totals ..	448	450	489	490	472	542	482	519

II. Placebo Given for the First Three Months and Sparine for the Latter Three Months

4 ..	32	32	32	32	32	32	32	32
7 ..	32	32	32	32	32	31	32	32
10 ..	25	20	24	32	21	24	26	10
11 ..	16	32	16	16	16	16	16	23
14 ..	16	15	16	16	16	16	16	16
16 ..	32	26	32	32	32	32	32	32
17 ..	21	2	21	2	29	2	20	2
20 ..	11	24	4	6	16	16	14	10
22 ..	26	24	26	24	26	24	26	32
23 ..	21	32	15	32	22	32	32	32
29 ..	5	2	6	Nil	3	4	10	Nil
31 ..	16	24	16	24	16	24	16	23
32 ..	22	32	20	32	20	32	26	32
33 ..	18	32	18	32	18	32	18	32
38 ..	32	32	32	31	32	31	32	29
41 ..	24	31	22	31	22	32	22	24
42 ..	23	8	23	18	23	9	18	4
43 ..	2	1	2	1	2	1	1	1
44 ..	31	26	31	22	31	29	32	32
45 ..	16	27	16	27	16	27	24	31
47 ..	19	24	19	24	19	24	22	20
Totals ..	440	478	423	466	444	470	467	449

It will be seen from this that there is no significant difference between the scores on Sparine and the scores on the placebo. The total scores for all patients are as follows:

Sparine 3,754 Placebo 3,775

The natural assumption from this is that Sparine medication produced no improvement in the patients, a conclusion which is completely contradicted by the overall assessment of the ward atmosphere and the opinion of the experienced nursing staff. In fact the ward changed from a closed one with degraded patients in special clothing and needing almost constant supervision to an open ward with the majority of the patients helping in ward tasks, going to occupational therapy, feeding and dressing themselves and with a very marked decrease in incontinence and unclean habits.

The apparent paradox is further stressed by study of the individual cases, and comparison of the charge nurse's report with the total daily score taken during the trial. The following are typical illustrations:

G.B., aged 47, admitted 1941

Charge nurse's report:

Before trial. Very aggressive epileptic, makes constant clicking noises with mouth and cannot hold a conversation. Stays in side room in strong clothes and is unoccupiable. Has the most degraded habits (eating faeces) and is always noisy and untidy.

Since trial, and continued on Sparine suspension. Now goes to occupational therapy where the therapist commends her neat sewing. Understands orders, watches TV, goes to the cinema, concerts and church. She is no longer incontinent or dirty but tends to hoard in a paper bag. She has stopped making clicking noises and is really quite a likeable person.

Results from Proforma:

	General Aggressive Behaviour	Over-Activity	Noisiness	Self-Care	Total
Placebo	25	24	21	26	96
Sparine	20	32	24	10	86

E.C.R., aged 65, admitted 1921

Charge Nurse's report:

Before trial. Patient throws everything on the floor and is constantly covering herself with faeces. Solitary, with no emotions, grossly untidy and needs constant supervision.

Since trial, and continued on Sparine suspension. Clean and tidy with much less supervision. No longer incontinent and sleeps quietly in an open dormitory without any of the night sedation needed previously.

Results from Proforma:

	General Aggressive Behaviour	Over-Activity	Noisiness	Self-Care	Total
Placebo	32	32	32	32	128
Sparine	32	31	31	29	123

M.E.B., aged 59, admitted 1933

Charge Nurse's report:

Before trial. A wanderer needing a good deal of supervision and always kept in strong clothes. Too untidy and erratic to do ward tasks and sometimes incontinent. Usually mute and unco-operative.

Since trial, and continued on Sparine suspension. Wears a tidy outfit to all social functions, works well in the kitchen with little supervision, baths and dresses herself and has been given an allowance for cigarettes, etc. She has also been given false teeth, glasses and a perm. She talks sensibly and eats her meals with a knife and fork, which she could not do before. Her visitors had previously stayed away because they were afraid of her, but now come regularly and take her out into the country.

Results from Proforma:

	General Aggressive Behaviour	Over-Activity	Noisiness	Self-Care	Total
Placebo	32	32	32	32	128
Sparine	32	32	32	32	128

E.A.B., aged 72, admitted 1932

Charge Nurse's report:

Before trial. Aggressive, over-active and incapable of conversation. Dirty and untidy with considerable supervision needed.

Since trial, and continued on Sparine tablets. Now seems almost normal. Clean and tidy, works on the ward and goes to church and to the cinema. Needs very little supervision.

Results from Proforma:

	General Aggressive Behaviour	Over-Activity	Noisiness	Self-Care	Total
Placebo	32	29	32	32	125
Sparine	26	26	18	17	87

These illustrative cases are typical of those showing a considerable discrepancy between clinical results and proforma ratings in the formal double-blind trial.

Twenty-eight patients who had improved with Sparine therapy in a clear and undoubted way were reconsidered and analysis of the proforma results showed that, according to the formal trial, four had improved on Sparine, 3 had equal ratings with Sparine and placebo and 7 had apparently improved on the placebo. This confirmed the misleading impression given by the formal trial with its day by day assessments of the patient.

Side-Effects

When on a dosage of 900 mg. Sparine daily thirteen patients showed mild parkinsonian symptoms accompanied by some degree of undue lethargy and retardation. Reduction of dosage to 600 mg. daily retained the clinical benefit and the extra-pyramidal symptoms regressed satisfactorily.

Epileptiform convulsions were noted in six patients but three of these suffered from epilepsy in addition to schizophrenia, and one patient had coincident general paralysis of the insane.

No cases of allergy or skin reactions were noted in either patients or in the nursing staff even though these had previously shown skin sensitivity to chlorpromazine.

Discussion

This assessment of liquid oral Sparine in chronic schizophrenics demonstrated the clinical effectiveness of the phenothiazine in over half of the patients. The improvement in these patients was clear cut and definite and, as a result, the management of these patients was made easier and the atmosphere of the whole ward improved. Many of the patients not included in the trial improved due to the change in their immediate environment.

This improvement in the trial subjects could not be found when the results of a formal double-blind trial were analysed which suggested that there was no significant difference between Sparine and the placebo.

Many criticisms have been levelled at the double-blind controlled trial in the past but, nevertheless, it has become accepted as the method of proving therapeutic efficiency of a drug. In this particular trial an attempt was made to overcome some of the more obvious shortcomings, such as fixed dosage regimes, short-term treatment and no allowance for latent periods of drug action but, even so, the results are clearly unrealistic and bear no relationship to the actual clinical change.

Many factors may have contributed to these contradictory results, including the prolonged benefit noted in the group that were given the placebo in the second half of the trial, which meant that improvement brought about by the active drug was still being recorded in the placebo period. In addition the general improvement in ward atmosphere brought about clinical change that was not directly attributable to the drug being taken. The biggest factor, however, is probably the impossibility of accurately recording change in patients who are being seen every day and who vary within limits at different times during the day. The assessing nurse or doctor cannot give a realistic appraisal of a patient's state on such a day-to-day basis and can only give a worth-while impression of clinical change when the patient's behaviour over a reasonable period is surveyed.

Despite the statisticians' delight in the double-blind trial, it is possible that a more useful idea of therapeutic activity in chronic psychotics is gained by a clinical evaluation after a reasonable period of therapy.

Summary

Due to skin sensitivity of the nursing staff to chlorpromazine, a single ward contained female chronic schizophrenics who had not been treated with phenothiazines.

A pilot trial on six patients showed marked improvement with a liquid preparation of Sparine (promazine hydrochloride) without affecting the allergic state of the nursing staff, so a double-blind trial in a further 50 patients was started. This consisted of three months therapy with Sparine and three months with placebo. Assessments were made daily and at the end of the study.

Fifty-six per cent. of the patients made a clear-cut clinical improvement on Sparine, but this impression was not sustained by the analysis of the results of the double-blind trial.

The possible reasons for this contradictory state of affairs are discussed.

Acknowledgments

I would like to thank Mr. H. W. Layer, Chief Pharmacist, for his tremendous help, the nursing staff for their patient co-operation, and John Wyeth & Brother Limited for supplying the active material.

References

Ayd, F. J., *N.Y. St. Med. J.*, 1957, **57**, 1742.
Azima, H., and Durost, H., *Canad. M.A.J.*, 1957, **77**, 671.
Brill, H., and Patton, R. E., *Amer. J. Psychiat.*, 1959, **116**, 495.
Fox, V., *Amer. Pract. Dig. Treat.*, 1956, **7**, 1461.
Goodman, D., and Cahn, M. M., *J. Invest. Dermatol.*, 1959, **33**, 27.
Graffagnino, P. N., Freil, P. B., and Zeller, W. W., *Conn. St. Med. J.*, 1957, **21**, 1047.
Mitchell, E. H., *J.A.M.A.*, 1956, **160**, 44.
Morgan, D. R., and Van Leent, J. P., *Med. J. Australia*, 1958, **11**, 696.
Usdin, G. L., *J. Louisiana St. Med. J.*, 1956, **108**, 251.

A COMPARATIVE TRIAL OF FOUR MONO-AMINE OXIDASE INHIBITORS ON CHRONIC DEPRESSIVES

By

T. J. N. BATES, M.A., M.B., D.P.M.

and

A. D. McL. DOUGLAS, M.B., D.P.H., D.P.M.

Saxondale Hospital, Nottingham

Depression is a serious illness in Western Europe and the United States of America. It is estimated that in 1957 the combined total of suicides in the United States, Britain, France and Western Germany was approximately 30,000 (1). The attempted suicide rate is considered to be six or seven times as great, which could give a grand total of 200,000 suicide attempts in that year in these countries. Many of these patients are depressives, as stated in a recent *British Medical Journal* leading article (2).

While electroplexy is still the treatment of choice for depression particularly in acute and suicidal types, nevertheless, it has some limitations. It fails to benefit certain cases and it has unpleasant side-effects, especially if it has to be administered over long periods. Some of the most troublesome side-effects are amnesia, E.C.T. phobia and possible organic changes with prolonged use. Administration of it can cause considerable disruption to the lives of the patients receiving it. This would apply in particular to those chronic depressives who often receive electroplexy over a long period of time. Consequently, any valid chemotherapy in the form of tablets would have marked advantages over electroplexy. Cerletti (3) would seem to have this in mind when he expressed the opinion that electroplexy was a trying treatment. It seemed, therefore, worth while to investigate the effect of four mono-amine oxidase inhibitors on a group of chronic depressives who had failed to respond satisfactorily to electroplexy or any other treatment. Most previous publications would seem to have been carried out with individual drugs of this group and to have been conducted on cases where the illness has been present for a relatively short time. We have only been able to discover two comparative trials involving mono-amine oxidase inhibitors (4, 5). A disadvantage in using the acute type of case is that there is a natural tendency towards remission during the first year, which is less likely to occur in the chronic depressive. Zubin (6) reported that 80 per cent. of patients discharged from mental hospitals do so by the end of the first year, thus indicating that any method will be more effective when tried on patients ill less than one year. The main purpose in conducting the present investigation was (*a*) to test the comparative efficacy of four known anti-depressant drugs on chronic depressives, (*b*) to ascertain whether any particular diagnostic category, symptom complex, age group or other factors would respond more readily and finally, (*c*) to evaluate the side-effects, if any, of these drugs.

Technique

The four mono-amine oxidase inhibitors chosen for the trial were β-phenylisopropyl hydrazine hydrochloride (Cavodil), iproniazide (Marsilid),

phenelzine (Nardil) and nialamide (Niamid). The trial was conducted according to the "Latin-square" technique using all 24 possible arrangements of the four drugs. The actual arrangements used were reasonably balanced as replacements had to be found, which resulted in increased numbers being used. Patients were on each drug for a period of five weeks with a two-week interval between each drug in order to minimize the possibility of cumulative side-effects. The following fourteen symptoms were taken as a rating scale; depressed mood, difficulty in thinking, psychomotor retardation, early morning wakening, morning accentuation of symptoms, hypochondriasis, self-deprecation, suicidal rumination, morbidity of outlook, agitation, inability to cope with duties, loss of interest, paranoid feelings and other symptoms. The presence of any of these symptoms was indicated by means of a tick and if they were present to a more marked degree, this was scored by means of one, two or three pluses, so that we were able to get a qualitative and quantitative estimation for each patient. Immediately prior to the trial each patient was rated by the psychiatrist normally in charge. During the course of the trial patients were seen weekly for an assessment of side-effects and any adjustment of dosage considered necessary. At the end of each five-week period the psychiatrist not normally in charge assessed the patient according to the above rating scale, so that ultimately each patient had four different ratings and the original assessment. The psychiatrist who had rated each patient then assessed them for the four different drugs, the following scale being used: recovered, much improved, improved, no change and worse. When each patient had completed the trial of the four drugs they were asked for a personal assessment using the same criteria.

Case Material

A total of 63 patients took part in the trial, 38 females, 25 males. Of this total nine failed to complete the trial of which six were females. Six of these cases required emergency electroplexy. The other three developed serious side-effects necessitating immediate termination. Fifty-four patients completed the trial and of these 42·6 per cent. were out-patients. The criteria for including patients in the trial was the presence of depression and a history of being under treatment for at least one year. Duration of illness varied fron 1 to 25 years. Eight men and eight women were known to have made at least one suicidal attempt. The diagnoses and age groups were as follows:

Age (Years)	Endogenous Retarded Depression	Endogenous Agitated Depression	Neurotic Depression	Atypical Depression	Schizo-Affective
30–39	4	–	3	1	–
40–49	3	1	5	2	–
50–59	7	2	3	6	1
60–69	7	7	3	2	–
70 and over ..	2	4	–	–	–
Total ..	23	14	14	11	1

By "atypical depression" is meant those patients with a good pre-morbid personality who develop phobic anxiety symptoms with depression as described by West and Dally (7).

Dosage

This was restricted to the optimum recommended dose by the manufacturers at the time the trial commenced, viz., Cavodil 12 mg. mane, Marsilid 50 mg. t.i.d., Nardil 15 mg. t.i.d. and Niamid 50 mg. t.i.d. The dosage was never raised above the recommended level, but was reduced in some cases, either temporarily or permanently because of the presence of side-effects. The patients received no other form of therapy while undergoing the trial except amylobarbitone gr. 3 at night if insomnia was marked.

Side-Effects

These were classified into two main categories (*a*) minor and (*b*) major.

Minor Side-Effects

	Cavodil	Marsilid	Nardil	Niamid
Elation	4	2	1	3
Drowsiness	1	–	6	3
Swollen face and ankles	2	6	3	1
Dry mouth	1	1	–	–
Hypotensive attacks	1	7	3	3
Paresthesia of skin	1	–	–	–
Twitching muscles	2	–	–	–
Difficulty in starting micturition	–	2	–	–
Weight increase	–	3	1	–
Erythema of arm	–	1	–	–
Mild confusional episode	–	1	–	1
Constipation	–	1	1	1
Insomnia	–	–	1	1
Increased appetite	–	–	1	–
Ataxia	–	–	1	–
Dyspepsia	–	–	–	1
Increased tension	–	1	3	–
	12	25	20	13

The above table enumerates the minor side-effects in relation to each drug.

Minor Side-Effects

It will be noticed that Iproniazide produces the greater number of side-effects, in particular mild hypotensive attacks which occur early in treatment and oedema chiefly of the ankles which occurred late. The main side-effect of Nardil was drowsiness, which tended to occur early. There were three cases of increased tension on this drug. Many of the symptoms remitted spontaneously after the first week or did so on reducing the dosage.

Major Side-Effects

Major Side-Effects

	Cavodil	Marsilid	Nardil	Niamid
Hypomania	–	2	3	1
Acute toxic confusional state	–	–	1	–
Jaundice	–	?1	?1	?1
	–	–	–	–
Total	–	2	4	1

The above table indicates serious side-effects. It will be noted that Cavodil did not, in this series, produce any major side-effects. The possible explanation

may be that the dosage was inadequate. Nardil was the drug that produced the greater number of major side-effects in contrast to Marsilid which was responsible for most minor ones.

Acute Toxic Confusional State

A female, aged 72, became confused after two weeks on Nardil, 15 mg. t.i.d. There were course tremors of the arms, clonic movements of the right leg and food refusal. At night she became acutely apprehensive, auditorily and visually hallucinated, maintaining that bombs were being dropped through the roof and dead bodies lying about the ward. The condition persisted for two weeks after the drug was discontinued.

Hypomania

This occurred in six cases, of which three were known manic-depressives (2 male, 1 female). In these three hypomanic symptoms persisted for as long as a month in spite of treatment. The other three consisted of two females and a male. In the case of the females the hypomanic state remitted within a week of withdrawal of the drug. The male, aged 64 with a diagnosis of retarded depression of 5 years' duration and no known history of hypomania, developed this condition after two weeks on Niamid. The symptoms persisted for 8 weeks despite heavy doses of Largactil. He finally discharged himself in a state of elation.

Jaundice

Female patient, aged 59, who started on Marsilid. The five-weekly interviews showed no evidence of side-effects except for a complaint of dizziness. This was followed by Niamid, during which time she showed no side-effects at the interviews. After one week on Nardil, she developed jaundice and complained of sickness, which she stated she first noticed while she was on Niamid. Bile salts and pigments were strongly positive in her urine and urobilinogen and urobilin were present in increased amounts. Liver function tests were as follows:

Van-den-Bergh Positive direct reaction
Total bilirubin = 5·0 mg. per 100 ml.
Alkaline phosphatase = 21 units per 100 ml.
Thymol turbidity = 3 units.
Thymol flocculation, Nil.
Zinc sulphate turbidity = 1 unit.
Zinc flocculation, Nil.
Total protein = 6·2 per cent.

Three weeks later:

Van-den-Bergh = Negative direct reaction.
Total bilirubin = 1·0 mg. per 100 ml.
Alkaline phosphatase = 17·5 units per 100 ml.

She discharged herself from hospital approximately 2 months from the time the jaundice was first noticed. This had cleared completely when she left the hospital.

DATA

Comparison of Whole Group

Comparison	Number With This Preference	Number With Opposite Preference	Equal Preference	Probability
Nardil better than Niamid ..	24	22	8	
Nardil better than Marsilid ..	27	15	12	$P<0\cdot1$
Nardil better than Cavodil ..	31	13	10	$P<0\cdot02$
Niamid better than Marsilid ..	22	19	13	
Niamid better than Cavodil ..	32	15	7	$P<0\cdot02$
Iproniazide better than Cavodil	27	15	12	$P<0\cdot1$

Comparisons for Patients Over 50

Comparison	Number With This Preference	Number With Opposite Preference	Equal Preference	Probability
Nardil better than Niamid ..	20	11	6	$P<0\cdot2$
Nardil better than Marsilid ..	20	8	9	$P<0\cdot05$
Nardil better than Cavodil ..	24	6	7	$P<0\cdot01$
Niamid better than Marsilid ..	14	16	7	
Niamid better than Cavodil ..	22	11	4	$P<0\cdot1$
Iproniazide better than Cavodil	21	8	8	$P<0\cdot05$

Comparisons for Patients Under 40
(7 males and 1 female)

Comparison	Number With This Preference	Number With Opposite Preference	Equal Preference	Probability
Niamid better than Nardil ..	7	1	–	$P<0\cdot1$
Niamid better than Marsilid ..	5	1	2	
Niamid better than Cavodil ..	7	1	–	$P<0\cdot1$

Data in Terms of Diagnosis

Diagnosis	Number	Mean Rank Preference (Lowest=Best) Cavodil	Marsilid	Nardil	Niamid
Endogenous retarded ..	18	2·9	2·6	2·1	2·3
Endogenous agitated ..	13	3·1	2·0	2·3	2·6
Neurotic depression ..	12	2·8	2·7	2·5	2·0
"Atypical depression" ..	9	2·7	2·5	2·3	2·5

Age Ranges at Which Drugs most Effective

Data divided into 30–40, 40–50, 50–60 and over 60 years ranges.

The best age range was 50–60 years.

This was *significantly better than over 60 years*, $P<0{\cdot}02$, and the 30–40 and 40–50 year ranges when the latter are compared *en bloc* with 50–60 years, $P<0{\cdot}05$ (when 30–40 year and 40–50 year range compared with 50–60 year range not quite significant).

Out-Patients Versus In-Patients

Out-patients did slightly better than in-patients, but the difference was not significant.

Patients' Assessment

	Cavodil	Marsilid	Nardil	Niamid
30–40 years	1·1	1·5	1·5	2·0
40–50 years	1·5	1·9	2·2	2·2
50–60 years	2·1	2·1	2·6	2·5
Over 60 years	1·2	2·4	2·5	2·2

Doctors' Assessment

	Cavodil	Marsilid	Nardil	Niamid
30–40 years	1·5	2·1	1·4	2·5
40–50 years	2·2	2·4	2·2	2·3
50–60 years	2·4	2·6	3·2	7·9
Over 60 years	1·7	2·2	2·7	2·2

The above tables show average results for different age ranges, using the following scores:

0 Worse; 1 No change; 2 Improved; 3 Much improved; 4 Recovered.

Comparison of Ten Most Successful Patients with Ten Least Successful: Notable Differences

	Number of Patients of Successful Group	Number of Patients of Unsuccessful Group
Age 50–60	6	–
Age 46–51	9	1
Depression more severe	2	6
Hypochondriasis more severe	2	4
Other symptoms: Insomnia	–	2
Hallucinated	–	1
Accentuation of symptoms A.M.	5	1

While the only difference that is significant is that with age, nevertheless "accentuation of symptoms in morning" and severity of the depressive mood could be important.

	Successful	*Unsuccessful*
Duration of illness, average	3·4 years	3·3 years

Further investigation of importance of "accentuation of symptoms in the morning" showed that this tended to be associated with the 50–60 age range, though not at a statistically significant level.

When all patients were investigated by ranking methods, keeping 50–60 years range, other ages, males and females separate, as four groups, and later combining for an overall test of significance, it was shown that "accentuation of symptoms in the morning" was significantly associated with success of drug treatment ($P<0\cdot05$).

Comparison of Responses to Particular Drugs with Particular Symptoms

It was not possible to observe any differences. The three best responses to individual drugs as above other drugs were investigated for Nardil, Marsilid and Niamid but no particular symptoms appeared to be associated with these patients. There were relatively few patients where one drug showed superiority over other drugs from both doctors' assessment, patients' assessment and where the response to the particular drug was also rated highly.

Discussion

The present trial, in common with other reports on mono-amine oxidase inhibitors (Ayd *et al.* (8); Vaisberg *et al.* (9); Beresford Davies (10)), fails to give any clear-cut indications as to the type of depressive illness benefited by these drugs. In this trial the outstanding fact is that the 50–60 age group showed the best response. This was statistically significant for all patients both above and below this age group. This may be in agreement with Middlefell (11) who, among his best results, mentions involutional menopausal depression in women and Beresford Davies (12) associated possible improvement with the older patient who had a long history of depression. The only symptom that was associated with success of treatment on a statistically significant level was "accentuation of symptoms in the morning" and although this symptom occurred more frequently in the 50–60 age group, it was not statistically significant for it. Hutchinson and Smedberg (13) consider that early morning wakening and inability to sleep were helped, but again this was not confirmed in the present trials. The clinical impression from this investigation was that insomnia and anxiety were not only unchanged, but in some cases aggravated. The "atypical" depressive group showed the best response to treatment and most of them were in the 50–60 age limit, although this did not reach statistical significance. This trend is in keeping with the report of West and Dally (14) who found Iproniazide to be of particular value in the treatment of "atypical" depression. Factors that were not significant in this trial were sex, duration of symptoms, whether in- or out-patient or any particular diagnostic grouping with the exception, as already mentioned, of a trend towards "atypical" depression. These observations appear to be in agreement with Ayd (15) who in a comparative trial of mono-amine oxidase inhibitors could find no relation to age, sex, duration or severity of patients' illness.

The drugs responded in the following order, (1) Nardil, (2) Niamid, (3) Iproniazide, (4) Cavodil for all ages. There was a more distinct preference in the over 50 age group. For patients under 40 years, Niamid appeared to be better than each of the other drugs although these differences were not always statistically significant. Comparisons between Cavodil and the other drugs reach a statistically significant level. The only other finding of statistical significance was in the over 50 age group, where Nardil was superior to Iproniazide. While the differences between Niamid and Nardil are not statistically significant at any age level, there was, nevertheless, a statistically significant

reversal in the position of these drugs with increased age, that is to say, relative to Nardil, Niamid is more effective in the younger patient. Further trends showed that Nardil appeared to be better with retarded and "atypical" depression while Niamid appeared more beneficial with neurotic depression. Procter (16) reports a similar experience with Niamid when he considers that this drug seems most useful in the treatment of neurotic depressive reaction in patients under 50. A slender preference was shown for Iproniazide in relation to agitated depression. Cavodil in this trial showed itself to be statistically of less value than the other three drugs. A possible explanation is that the dosage of this drug used in the trial was insufficient. Ayd (17) believes that patients who fail to respond to one of these anti-depressant drugs seldom respond more than partially to another. Our findings are in disagreement with this. The clinical impression in this trial was that if patients were going to respond to the drugs favourably they did so by the end of the second week. Harrington and Imlach (18) reported a similar period of time for improvement with Nardil. A disturbing impression also noted by Ayd (19) was that patients who had made an initially good response to one of these drugs did not always continue to do so, if the drug had been withdrawn and later re-instituted.

There is no doubt that elation and even hypomania are not uncommon side-effects with these drugs, particularly in the manic depressive group. Because of this patients should be seen frequently and dosage reduced or withdrawn if elation is present. The acute toxic confusional state occurred with Nardil and as this was the first mono-amine oxidase inhibitor the patient received, there could be no possibility of cumulative side-effects. Johnson and Eilenberg (20) described a similar case with Nardil. The case of jaundice could not be attributed to any one particular drug, with the exception of Cavodil which the patient did not receive. Cumulative side-effects may have been responsible. Attention is drawn to two cases where because of markedly increased tension the trial had to be terminated. The drug in question was Nardil. Altogether four cases of increased tension were noted. From these observations it would appear that anxiety is not helped by these drugs, or that in cases where this symptom is marked, a suitable drug for anxiety should be given. No explanation can be offered why patients in the 50–60 age group did best, but it may be that an involutional factor is involved. In conclusion, from the statistical evidence it can be assumed the drugs influenced chronic depression because in the experiment there were systematic differences between the drugs—in other words the less successful drugs served as controls for the more successful.

In retrospect there were six cases (four female and two male) where some doubt could be placed on the exact diagnosis, as to whether they were neurotic depressive reactions or simply "neurotics". A study of the ten patients who showed the poorest response included this doubtful group presenting with marked tension, frequent phobic symptoms and many somatic complaints. Depression was variable and inconstant. The pre-morbid personality was hysterical and inadequate in all cases.

Summary

A comparative trial of four mono-amine oxidase inhibitors on chronic depressives resistant to other forms of treatment is described. The 50–60 age group showed the best response to treatment. The only symptom associated with success of treatment at a statistically significant level was "accentuation of symptoms in the morning". Nardil was the beneficial drug, particularly in the

over 50 age group; Niamid most effective for patients under 40 and Cavodil in the dosage used was inferior to the other drugs. The commonest major side-effect was hypomania. A case of jaundice and one of toxic confusion is also described. It is considered that the mono-amine oxidase inhibitors are of definite therapeutic value in the treatment of depression especially in chronic depressives resistant to other forms of treatment.

References

1. *Epidemiological and Vital Statistics Report*, 1959, Vol. 21, No. 10.
2. *Brit. Med. J.*,, 1960, 178. January 16.
3. Impastato, D. J., "Symposium at American Eastern Psychiatric Research Association Inc."
4. Ayd, F. J., *Psychosomatics*, 1960, **1**, 27.
5. Linford Rees, W., *Nature*, 1960, **186**, 114–120. April 9.
6. Smith, J. A., "Symposium at American Eastern Psychiatric Research Association, Inc."
7. West, E. D., and Dally, P. J., *Brit. Med. J.*, 1959, 1491. June 13.
8. Ayd, F. J., *et al.*, *ibid.*
9. Vaisberg, M., *et al.*, *ibid.*
10. Beresford Davies, E. Unpublished material.
11. Middlefell, R., Symposium on Depression, at Royal College of Surgeons, May 27, 1960.
12. Beresford Davies, E., Unpublished material.
13. Hutchinson, J. T., and Smedberg, D., *J. Ment. Sci.*, 1960, **106**, 704.
14. West, E. D., and Dally, P. J., *Brit. Med. J.*, 1959, 1491. June 13.
15. Ayd, F. J., *Psychosomatics*, 1960, *1*, 27.
16. Procter, R. C., Symposium at American Eastern Psychiatric Research Association Inc.
17. Ayd, F. J., *Psychosomatics*, 1960, **1**, 27.
18. Harrington, J., and Imlach, N. W., Symposium on Depression, at Royal College of Surgeons, May 27, 1960.
19. Ayd, F. J., *Psychosomatics*, 1960, **1**, 27.
20. Johnson, J., and Eilenberg, M. D., *Brit. Med. J.*, 1960, 857. September 17.

A CLINICAL TRIAL OF IMIPRAMINE ("TOFRANIL") ON DEPRESSED PATIENTS

By

W. ROSS ASHBY, M.D., D.P.M.

*Research Professor**

University of Illinois, Urbana, Illinois, U.S.A.

and

G. H. COLLINS, M.D., D.P.M.

Consultant Psychiatrist†

Kingsway Hospital, Derby

Recently many new anti-depressive drugs have flooded the market, the objective being initially to assist and finally to replace E.C.T. as the treatment of choice for depressive states. One such preparation is Tofranil (N-(γ-Dimethyl-aminopropyl)-iminodibenzyl hydrochloride or imipramine). It was first favourably reported on by Azima (1) and Kuhn (2).

This drug was tried on a series of chronic depressed patients at Barnwood House, most of them being sufficiently unchanging in their depression to make it likely that little change was to be expected spontaneously over a period of some months.

Method

The "double-blind method" was used with placebo tablets exactly resembling the Tofranil ones. The tablets were issued by the dispenser in such a manner that neither patients nor the assessing physician knew which were being given.

Every patient was given a full course of the placebo and a similar one on Tofranil, the following sequence of 25 mg. tablets being strictly adhered to:

1	tablet	t.d.s. for	3 days
2	tablets	t.d.s. for	3 days
3	tablets	t.d.s. for	3 days
4	tablets	t.d.s. for	3 days
3	tablets	t.d.s. for	3 days
2	tablets	t.d.s. for	42 days
1	tablet	t.d.s. for	7 days

A week without tablets was left between the two courses, each of which was of nine weeks' duration. When a patient was included in the series, the question as to whether Tofranil or placebo should be given first was decided by chance.

The assessment of each patient's clinical condition was carried out by means of a standardized scale which was duly completed at the following times:

1. Before the first course;

* Formerly Medical Director, Burden Neurological Institute, Bristol.
† Formerly Deputy Medical Superintendent, Barnwood House, Gloucester.

2. Just before the end of the first course, while the patient was still on the drug (or placebo);
3. At one week after the end of the first course (this occasion being also "Before the second course");
4. Just before the end of the second course;
5. At one week after the end of the second course.

A copy of the standardized rating scale is attached (Appendix I); it assessed the patient's state according to:

1. Degree of depression.
2. Amount of activity, as retardation or agitation.
3. The presence of delusions.
4. The presence of hallucinations.
5. The amount of sleep, either with sedative or without.
6. Amount of appetite.
7. Range of interests.
8. Degree of sociability.
9. Amount of nursing required.

Each of these nine variables was assessed at one degree of normality and four degrees of abnormality. One point for each degree of abnormality in each of the nine criteria gave a scale varying from 0 to 36 points measuring the "degree of clinical abnormality". We are satisfied, from practical experience of it, that it gave an estimate of as much accuracy as can reasonably be expected in psychiatric practice.

The markings at the five assessments are shown in Tables I and II below. Fifteen patients only completed the clinical trial out of twenty-two who were originally selected. Of the number who failed to complete the trial three died of causes quite unrelated to the treatment, and four refused to continue because of side-effects. This small group will be discussed separately.

TABLE I

Assessment

	First	2	3	4	Final
Patients receiving Tofranil first	10	7	12	14	6
	12	10	9	10	10
	11	11	11	10	11
	18	15	11	16	10
	4	5	2	2	3
	9	10	9	7	8
	14	11	13	13	11

TABLE II

	First	2	3	4	Final
Patients receiving placebo first	7	11	4	1	12
	18	11	15	11	16
	18	11	14	13	12
	8	10	15	14	12
	11	10	10	12	10
	14	14	19	18	15
	15	13	12	10	10
	18	16	13	15	14

As stated above, only fifteen patients completed the clinical trial. In the Tables, their order has been re-arranged so as to bring together all those who had Tofranil first (Table I) and those who had placebo first (Table II). Each row in the Tables refers to one patient, and the score records "degrees of clinical abnormality", so that a decrease corresponds to an improvement in the clinical condition.

In addition to this objective but somewhat insensitive method of scoring, one of us (G.H.C.) kept regular records of the patients' general clinical condition, while also remaining ignorant of the type of tablet which was being given.

The Results

Simple inspection of the Tables shows that no factors are grossly effective, although the final readings of all the patients who were given Tofranil first (Table I) were uniformly lower than those at the first assessment, indicating some terminal improvement over the whole course. In Table II the final assessments were less frequently lower than the ones made at the initial assessment. The exact statistical significance of these differences between the two groups is uncertain, so we proceed to more sensitive statistical tests for changes on the average.

Examination shows that the most evident effect is that caused by just putting the patients on to "a tablet", for, though hardly significant, the first assessment (column 1) made before the patients actually commenced treatment, has a somewhat higher average than those of the others. The averages are, respectively:

$$12{\cdot}5,\ 11{\cdot}0,\ 11{\cdot}3,\ 11{\cdot}1,\ 10{\cdot}7$$

(The slight lack of orthogonality is not sufficient to cause appreciable disturbance here.)

This drop in the score of "degrees of clinical abnormality", suggests that clinical improvement invariably followed after administration of a tablet, regardless of whether this was Tofranil or placebo.

In view of this effect, which was at least as large as any other detectable effect, it seems simplest to compare the effects of Tofranil and placebo in the following ways:

(*a*) The two compared for the effects produced during the first seven weeks of the first course, i.e. by columns 1 and 2.

(*b*) The two compared for the effects produced during the first seven weeks of the second course, i.e. by columns 3 and 4.

In this way we obtain two independent comparisons, each in fairly homogeneous conditions. By making each patient his own control, the heterogeneity in the levels of depression (some patients with high scores throughout, some with low) can be eliminated. The *changes* induced by the tablets, all in the first course, were then as follows:

(*a*) Due to Tofranil: $-3, -2, \ 0, -3, +1, +1, -3.$

(*b*) Due to placebo: $+4, -7, -7, +2, -1, \ 0, -2. -2.$

The two distributions may both be displaced from zero by all those factors that make the second column different from the first, but the *difference* between their means can only be due to the drug difference t proves to be $+0{\cdot}21$, so there is no significant difference.

The same comparison can be made for the second course, and here the changes were:

(*a*) Due to Tofranil: −3, −4, −1, −1, +2, −1, −2, +2,

(*b*) Due to placebo: +2, +1, −1, +5, 0, −2, 0.

t is −1·50—again the effect is not of great significance, though in the right direction.

As the series is small and no main effect can be seen, further analysis lacks justification.

The method of assessment, however, tends to be somewhat insensitive and the more delicate perceptions of the clinician have more to report. Of the fifteen patients who completed the trial, eight were reported by him as "more settled" when on Tofranil, but none were reported as being clinically improved while on placebo. Treatment with Tofranil was continued with good effect on the eight patients noted above after the end of the clinical trials.

Side-Effects

These were complained of by four patients in the group and all discontinued treatment within three weeks of commencement. It is to be noted that three of these cases were in the same ward, were friendly, and were in close contact with each other. One after the other within a period of a few days they all made similar complaints, namely of dryness of the mouth, tachycardia, and tremulousness of the lower limbs affecting their gait. All were over seventy years of age. The fourth patient was much younger and refused to continue the tablets after 3–4 days, claiming that they made her giddy.

Summary

Fifteen depressed patients were given a nine-weeks course of Tofranil, on a double-blind system with a similar course on facsimile placebo tablets. Some were given the placebo course first and some the Tofranil.

Survey of the results suggests that the drug had some effect in making the patients more settled. The effect, however, could not be shown significantly on a planned marking scale.

Mention is also made of the side-effects which were encountered.

Acknowledgments

Our thanks are due to the ward sisters and charge nurses, and particularly to Sister Edwards, without whose willing help and co-operation the clinical trial would not have been completed.

We would also like to thank the medical department of Geigy Pharmaceutical Company Limited for their unfailing courtesy and their help in supplying Tofranil and placebo tablets for use throughout the clinical trial.

References

1. Azima, H., and Vispo, R. H., *Amer. J. Psychiat.*, 1958, **115**, 245.
2. Kuhn, R., *ibid.*, 1958, **115**, 459.

Appendix I

Depression Rating Scale

Name..... Age..... Date of Marking.....

Depression	Absent	Slight	Moderate	Severe	Remarks
Activity:					
(*a*) Retardation ..	Absent	Slight	Moderate	Severe	
(*b*) Agitation ..	Absent	Slight	Moderate	Severe	
Delusions	Absent	Slight	Moderate	Severe	
Hallucinations ..	Absent	Slight	Moderate	Severe	
Sleep:					
(*a*) With drugs ..	Over 7 hours	5–7 Hours	3–5 Hours	0–3 Hours	
(*b*) Without drugs	Over 7 hours	5–7 Hours	3–5 Hours	0–3 Hours	
Appetite	Normal	Poor	Needs coaxing	Has to be fed	
Interests	Normal	Limited	Needs coaxing	None	
Sociability	Normal	Reserved	Withdrawn	Inaccessible	
Nursing required ..	None	Slight	Considerable	Constant	
Suicidal	No			Yes	

A CONTROLLED TRIAL OF IMIPRAMINE ("TOFRANIL") IN THE TREATMENT OF SEVERE DEPRESSIVE STATES

By

LINFORD REES, M.D., B.Sc., F.R.C.P., D.P.M.

Physician-in-Charge

Department of Psychological Medicine, St. Bartholomew's Hospital

Consultant Physician

Bethlem Royal and the Maudsley Hospital, London

A. C. BROWN, M.A., M.B., B.Chir.

Registrar

Bethlem Royal and the Maudsley Hospital

and

S. BENAIM, M.B., M.R.C.P., D.P.M.

Consultant Physician

Halliwick Hospital

The discovery by Kuhn (1957) that an iminodibenzyl derivative (imipramine) was therapeutically successful in depressive illnesses aroused great interest and stimulated clinical trials with the drug in many parts of the world. The results of some of the published reports are given in summarized form in Table I.

Very few of the published reports however are based on adequately controlled trials.

In a critical review of the place of drugs in the treatment of depression Rees (1960) emphasizes that fully-controlled double-blind procedures were indispensable for trials of drugs in psychiatry. Otherwise, results will be vitiated by manifold sources of error, e.g. changes in clinical state during the trial period being due to factors either in the environment or in the individual acting quite independent of the pharmacological actions of the drug under trial. Other sources of error are the biased allocation of active and control medication and bias in recording and reporting clinical changes, unless double-blind conditions are used.

Design and Methodology of the Trial

1. *Criteria for inclusion in trial.* Only patients who had depressive illnesses conforming to clear diagnostic criteria agreed and set out before the trial were included. A further criterion for inclusion was that the patient would be considered suitable to electroplexy. The trial was confined to in-patients as this permitted adequate supervision of tablet administration and offered much

TABLE I

Author	Number of Patients Studied	Type of Illness	Total of All Grades of Improvement %	Full Remission or Marked Improvement %	Slight Improvement %	Type of Illness Responding Best
Kuhn (1958)	500	Various diagnostic categories	70–80 of Endogenous depression			Endogenous depression
Keilholtz and Battegay (1959)	69	Severe depressive illnesses	84	61	23	Endogenous depression
Lehmann *et al.* (1958) ..	84	Depressive states: 60% endogenous; 40% other types	90	65	25	Endogenous depression
Fazio, Giberti and Loeb (1958)	75	Various types of depression	73·4			Recurrent depression
Sloane *et al.* (1959)	30	Endogenous depressions suitable for E.C.T.	80			
Saucier and Dumas (1959) ..	76	Out-patients with various types of depression	57	35	22	
Hoff (1959)	50	Endogenous depression	66	22	40	Inhibited type of endogenous depression
Azima (1959)	100	Neurotic depression (38) Psychotic depression (44)	82	44	38	
Delay and Deniker (1959) ..	137	Various forms of depression	60	22	38	Recurrent depression Involutional depression
Ball and Kiloh (1959)	49	Endogenous depression (27) Reactive depression (25)	74 59	— —	— —	
Mann and MacPherson (1958)	70	Depressed patients attending General Hospital	80	63	17	Endogenous depression

better opportunities for assessing changes in clinical status than would be possible with out-patients.

Patients were first observed for about 8–14 days during which time any special investigations which were needed in a patient were carried out. Patients who showed signs of spontaneous improvement during the observation period were not included, in order to avoid this obvious source of error.

2. *Triple-blind control.* Patients, nurses and physicians responsible for recording changes were not informed when inert and active tablets were being administered. The batches of tablets were coded by two series of random numbers by the pharmacist who retained the key to the code. The inert tablets used were identical in size, colour and appearance as imipramine tablets. Tablets were given uncrushed to prevent recognition by taste.

The results were fully recorded and analysed before the code was broken, making the trial "triple blind".

3. Active and inert tablets were given to each patient for two or three weekly periods. The allocation of active and inert tablets for the initial period was carried out by a randomizing procedure. During the second three-weekly period the alternative preparation was given. The method of using the patient as his own control eliminates the difficulty of matching patients into pairs or groups. The method of random allocation on inert and active tablets for the initial period eliminates selection errors. The different sequences of administration of active and inert tablets equalizes the chances of spontaneous improvement, or other factors which might influence the patient's clinical state, occurring with the inert tablets as with the active tablets.

4. *Recording changes in clinical state.* A number of clinical features relating to depressive illness were rated by physicians on a 5-point scale according to severity.

Separate records were made of nurses' observations which covered the 24-hour period and also of patients' reports.

An overall grading of the patient's clinical state was made by physicians at weekly intervals.

The ratings and gradings made at the end of the third week and at the end of the sixth week were the ones chosen for statistical comparison of the effects of active and inert tablets. This procedure was adopted as experience, in a pilot trial, showed that the beneficial effects of imipramine often take two or three weeks to develop and that ratings and gradings made at the end of the three-week period would give the best measure of the effectiveness of the drug given for the period. The method also has an additional advantage in that it avoids errors due to "carry over" effects of the active drug into an ensuing "inert tablet" period.

5. *Statistical methods.* As the usual parametric statistics are not suitable for dealing with data derived from ratings and gradings, non-parametric statistics were used, in particular Wilcoxon Matched Pairs Signed Ranks Test (Siegel, 1956). Non-parametric methods also have a special advantage in permitting statistical comparison of individual items separately for assessment of any differential effects the drug may have on symptoms and other clinical features of the illness.

Dosage

Imipramine and inert tablets were given according to the schedule advised by the manufacturers as follows:

TABLE II

	Sex and Age of Patient	Family History of Psychiatric Illness	Previous Attacks of Depression	Duration of Present Illness (Weeks)	Imipramine Grade and Weighting at End of 3 Weeks	Inert Tablets Grade and Weighting at End of 3 Weeks	Difference in Weights		Side-Effects
							Imipramine	Inert	
A:									
1	F 30	0	0	236	+2	+1	+1		Rash
2	M 57	0	1	20	+2	0	+1		Tremor, dryness of mouth
3	M 45	+	3	6	+2	0	+1		Excessive sweating
4	F 28	0	3	6	+3	0	+3		Dry mouth
5	F 57	0	1	6	+2	0	+2		Nil
6	F 41	+	3	53	+2	−1	+3		Nil
7	F 65	+	3	104	+1	0	+1		Nil
B:									
8	M 60	0	1	52	+3	+3	0		Sweating, flushing
9	F 56	+	2	32	+1	+1	0		Indigestion—Inert tablets
10	M 39	0	1	60	+1	+3		+2	Tremor—Inert tablets
C:									
11	M 63	+	3	104	0	0			Nil
12	F 44	+	2	22	0	0			Nil
13	F 54	0	0		0	0			Nil
14	F 71	+	3		0	0			Nil
15	F 68	+	4	6	0	0			Indigestion—Inert tablets
16	M 38	0	1	200	0	0			Constipation, dry mouth, sweating
17	F 62	0	1	80	0	0			Nil
18	F 39	0	5	14	0	+1		+1	Nil
19	F 24	0	0	2	0	0			Nil
20	F 38	0	2	200	0	+1		+1	Blurring of vision. Giddiness. Flushes, sweats

For the first two days four 25 milligram tablets and then the tablets were increased by two 5 milligram tablets daily to reach 10 tablets on the fifth day. This was continued for five days and then gradually reduced by one tablet daily to 6 tablets a day, which was continued until the 21st day.

Results

Clinical Data

Table II gives data on the group of 20 patients participating in the treble-blind trial. The group consisted of 14 women and 6 men with ages distributed as follows: 20–29 years, 10 per cent.; 30–39 years, 25 per cent.; 40–49 years, 15 per cent.; 50–59 years, 20 per cent.; 60–69 years, 25 per cent.; 70 years and over, 5 per cent.

Eight patients (40 per cent.) had a family history of psychiatric illness in first degree relatives.

Seventeen out of the 20 patients had had previous attacks of depression ranging in the number of previous attacks from one to five and amounting to 39 in all. Nine of the seventeen patients who had previous attacks of depression had been successfully treated by E.C.T. with recovery from the attack.

Comparison of Results Obtained with Imipramine with Those Obtained with Inert Tablets

Table III gives the percentage distribution of the clinical gradings made at the end of the third week of imipramine and at the end of the third week

Table III

Clinical Grading	Weighting of Grade	Imipramine %	Inert Tablets %
Total remission of symptoms	+3	10 } 35	10 } 10
Marked improvement ..	+2	25 }	0 }
Moderate improvement ..	+1	15	20
Slight or no improvement ..	0	50	65
Slightly worse	−1	0	5
Moderately worse	−2	0	0
Markedly worse	−3	0	0

with inert tablets. It will be seen that the most marked difference occurring between active and inert tablets is in "marked improvement" grade with imipramine having 25 per cent., inert tablets none.

Comparing the two highest levels of improvement (Grades 1 and 2), the figure for imipramine = 35 per cent. and for inert tablets 10 per cent. The difference is statistically significant at 5 per cent. level of confidence.

Table II gives the weights attached to the respective grades of improvement with imipramine and inert tablets. Ten patients (Sections A and B of the table) improved with imipramine tablets, of these seven patients (Section A) did better on active than inert tablets, the sum of the weights in favour of imipramine being 12. Three patients did better on inert tablets than imipramine the difference, however, being slight, the sum of weights favouring inert tablets being 4. Two improved to an equal extent with active and inert tablets and 8 to neither.

Our findings clearly indicate that imipramine has a significantly greater beneficial effect on severe depressive illnesses than that associated with inert tablets.

It was deemed desirable to compare the status of the group at the end of the third week with that at the end of the sixth week irrespective of the type of tablet received. No significant difference was found so that this possible source of error was not relevant in this study.

Changes in Individual Clinical Features with Imipramine and Inert Tablets

Table IV shows the following features which responded statistically better with imipramine than with inert tablets.

(1) Depressive appearance and behaviour, (2) depressive thought content, (3) insomnia, (4) anxiety.

Table IV

Features which were Significantly Improved with Imipramine

Ratings	Statistical Significance of Differences
Physicians' rating:	
Depressive appearance and behaviour ..	P. between ·05 and 0·2
Depressive thought content	P. = ·01
Insomnia	P. between ·05 and 0·2
Anxiety	P. < ·01
Patients' reports:	
Anxiety	P. > ·01
Insomnia	P. = ·01

Statistical evaluation of patients' reports revealed significantly greater improvement in anxiety and insomnia with imipramine than with inert tablets.

No significant differences in physicians' ratings between active and inert tablets occurred in the following features, retardation, hypochondriasis, anorexia, paranoid ideas.

Recurrence of Symptoms with Inert Tablets Following Improvement with Imipramine

Additional evidence indicating that the clinical improvement occurring with imipramine is safely attributable to its pharmacological actions rather than to extraneous factors, is provided when improvement occurs with imipramine and is followed by relapse during the ensuing period of inert tablet administration. If improvement again occurs when the drug is re-introduced and is followed again by a relapse on inert tablets, the therapeutic activity of the drug in these patients would be unequivocably established.

Eleven patients were allocated the drug first by a process of randomization. Of these two improved with imipramine and relapsed in the ensuing inert tablet period and improved again subsequently with imipramine after the completion of the double-blind trial.

Comparison with Electroplexy

Of the seven patients who improved to a greater extent with imipramine than inert tablets, two had received E.C.T. earlier in the illness without benefit.

Two patients who did not benefit from imipramine had to have E.C.T. which produced a speedy and full recovery.

Side-Effects

Seven patients showed side-effects on imipramine and three others with inert tablets.

The side-effects most commonly seen in the series with imipramine were dryness of the mouth, excessive sweating and flushing. In individual patients skin rashes, constipation, blurring of vision and giddiness occurred.

Side-effects with inert tablets included indigestion in two patients and tremor in one.

No toxic reactions were observed.

Discussion

Although our investigation provides conclusive statistical evidence that imipramine has significant beneficial effects on some severe depressive illnesses, the results achieved are not as good as those reported in the literature generally which give improvement rates ranging from 57 per cent. to 92 per cent. Excluding slight improvement which is of minor significance in practice, the range is from 22 per cent. to 65 per cent. The total percentage of moderate, marked and total improvement in our series is 50 per cent. Taking total recovery and marked improvement only the figure is 35 per cent.

The following are possible reasons for the differences in findings:

1. Our group consists entirely of severe depressive illness which may respond less well to imipramine than milder depressions.

2. The period of treatment was limited to six weeks in all, with three weeks on active tablets.

3. Our controlled methods excluded those sources of error which might otherwise have given false high improvement rate.

In connection with (1) it will be of interest to quote the results of an uncontrolled trial of imipramine on less severe depressive illness in out-patients. This group comprises 30 per cent. predominantly endogenous and 70 per cent. predominantly reactive or neurotic depression.

The results in this group were Grade 1, 25 per cent.; Grade 2, 33 per cent.; Grade 3, 25 per cent.; Grade 4, 35 per cent.; Grade 5, 5 per cent. The endogenous depressions had a slightly higher improvement rate than the predominantly reactive depressions.

These results are more similar to the results of uncontrolled trials reported in the literature but all three factors may have contributed to the results in this uncontrolled series.

In the patients who were not improved with imipramine and were given electro-convulsive therapy the improvement was so marked and clear-cut in time that there was no doubt of the superiority of electro-convulsive therapy in these patients. As only a proportion of depressive illnesses respond to imipramine treatment and these include both endogenous and reactive varieties there is an urgent need for further research into the attributes of the individual, whether these prove to be clinical, psychological, physiological or biochemical which are highly correlated with susceptibility to imipramine, in order to achieve more efficient selection and correspondingly better therapeutic results.

References

Azima, H., *Canad. Med. Ass. J.*, 1959, **80**, 535.
Ball, T. R. B., and Kiloh, L. G., *Brit. Med. J.*, 1959, *ii*, 1052.
Delay, J., and Deniker, P., *Canad. Psychiat. Ass. J.*, 1959, **4**, 100.
Fazio, C., Giberti, F., and Loeb, C., *Minerva Med. (Torino)*, 1958, **49**, 3143.
Hoff, H., *Canad. Psychiat. Ass. J.*, 1959, **4**, 55.
Keilholtz, P., and Battegay, R., *Schweiz. Med. Wschr.*, 1959, **88**, 763.
Kuhn, R., *ibid.*, 1957, **87**, 1135.
Idem, *Amer. J. Psychiat.*, 1958, **115**, 459.
Lehmann, H. E., Cahn, C. H., and de Verteuil, R. L., *Canad. Psychiat. Ass. J.*, 1958, **3**, 155.
Mann, A. M., and McPherson, A. S., *ibid.*, 1958, **4**, 38.
Rees, L., *Nature*, 1960, **186**, 114.
Sloane, R. B., Habib, A., and Batt, U. E., *Canad. Med. Ass. J.*, 1959, **80**, 540.
Iidem, *Canad. Psychiat. Ass. J.*, 1959, **4**, 126.
Saucier, J., and Dumas, C. L., *Canad. Psychiat. Ass. J.*, 1959, **4**, 148.
Seigel, S., *Non-Parametric Statistics*, 1956. New York: McGraw Hill.

A CONTROLLED TRIAL OF PHENELZINE ("NARDIL") IN THE TREATMENT OF SEVERE DEPRESSIVE ILLNESS

By

LINFORD REES, M.D., B.Sc., F.R.C.P., D.P.M.

Consultant Physician

Bethlem Royal and the Maudsley Hospital

Physician-in-Charge

Department of Psychological Medicine, St. Bartholomew's Hospital, London

and

BRIAN DAVIES, M.D., B.Sc., M.R.C.P., D.P.M.

Senior Registrar

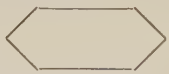
Bethlem Royal and the Maudsley Hospital

THE pharmacological treatment of depression was quite limited in efficacy before the discovery of iproniazid and imipramine (Rees, 1960).

Iproniazid, although therapeutically effective in some depressive illnesses, was found to have serious toxic effects, as reported by De Verteuil and Lehmann (1958), Fisher and Olver (1958), Smarr *et al.* (1958), Weiss *et al.* (1958), Zetzel and Kaplan (1958), Frantz (1958), Shay and Sun (1958), Benaim and Dixon (1958).

Iproniazid has a potent monoamine oxidase inhibiting action, and as this was believed to be related to its beneficial therapeutic effects on depression research was directed to other monoamine oxidase inhibiting drugs with the aim of discovering safer and more effective pharmacological agents for treating depression. A number of new monoamine oxidase inhibiting drugs have recently been introduced, one being phenelzine.

Phenelzine is phenyl methyl hydrazine sulphate, with the following formula:



Results of some trials with phenelzine are given in Table I.

It is unfortunate that only some of the published reports on phenelzine deal with adequately controlled trials.

Among the manifold sources of error which often vitiate results of uncontrolled trials are those due to:

1. Bias in selection and allocation of active and inert tablets either to patients or to groups.
2. Bias and anticipation in the reporting and recording changes when patient or observers know when active and inert tablets are being given.

TABLE I

Author	Number Investigated	Clinical Composition of Group	Percentage Improvement All Grades	Percentage Marked Improvement
Thal (1959)	180	Depressive illnesses (various)	100	80
Sainz (1959) ..	122	Endogenous depression	85	85
King (1959) ..	13	Severe depressive illnesses	69	Not stated
Furst (1959) ..	36	Out-patients with depressive illnesses	69	Not stated
Dickel *et al.* (1959)	85	Depression following chronic tension and fatigue	80	80
Dunlop (1959) ..	50	Out-patients with depressive illness	82	82
Sarwer-Foner *et al.* (1959)	60	Depression in in-patients and out-patients	55	Not stated
Hutchinson and Smedberg (1960)	34	In-patients (female) with depression	79	38

3. The possible beneficial therapeutic effects of suggestion or produced by the regime of the new treatment or resulting increased medical and nursing attention naturally associated with any trial.

4. The possibility that changes in clinical state during the trial may be due wholly or partly to spontaneously occurring improvement or exacerbation; or to manifold other factors either in the person or his environment.

Design of Present Trial

1. *Criteria for inclusion in the trial.* Only patients suffering from depressive illnesses conforming to diagnostic criteria agreed and set down before the beginning of the trial, were accepted for the trial. The group studied consisted of 20 patients so selected, successively admitted to the Bethlem Royal Hospital.

2. *Preliminary observation.* All patients were observed and investigated for 8–14 days following admission in order to ascertain and assess the extent of any fluctuations in clinical state. Any patient showing clear evidence of spontaneous improvement from the depressive illness during this period was excluded in order to eliminate this source of error.

3. *Patients as self controls.* As accurate matching of psychiatric patients is virtually impossible, it was decided to adopt the method whereby the patient acts as his own control. This method effectively overcomes the difficulties of matching and is especially suitable for drug trials in psychiatry.

4. *Triple-blind control.* It was deemed a *conditio sine qua non* that the trial should be fully blind in order to eliminate errors due to suggestion, anticipation or bias in the reporting or recording of clinical changes which undoubtedly would tend to occur if either patients or observers knew when the active and inert preparations were being given.

Inert tablets, identical in size, colour and appearance to the phenelzine tablets, were used for control purposes. Tablets are given uncrushed to avoid recognition by taste. The batches of inert and active tablets issued from the dispensary were coded by the pharmacist by means of two series of random numbers.

As a final precaution the results were fully analysed before the code was broken, making the trial, in effect, "triple blind".

5. *Method of random allocation and sequence control.* In order to deal with the possibility that some, or possibly all, the changes in clinical state of patients during the trial might be due to spontaneous improvement or to other factors unconnected with the pharmacological properties of the drug, the following methods were used:

(*a*) The allocation of inert and active tablets for the first three-weekly period was achieved by a randomizing procedure.
(*b*) During the second three-weekly period the alternative preparation was given.

This method provides a chance probability that approximately half the patients should start with the active drug and half with inert tablets. The procedure of random allocation for the first period effectively eliminates selection errors. The different sequences of administration of active and inert tablets in the two halves of the group equalize the chances that extraneous factors which are capable of influencing clinical state will be acting concurrently with the inert tablets as with the active tablets.

Dosage. The tablet dosage was two, three times a day, giving a daily dosage of active drug of 90 mg.

6. *Item and Record Sheets:* (a) *Rating Scales.* A series of clinical features were rated by the physicians, on a five-point scale, according to severity.

Ratings were made immediately before the trial and at weekly intervals thereafter for six weeks.

A twenty-four hour record of behaviour and clinical state was made by the nursing staff and was recorded on separate record sheets.

The sum of physicians' ratings provide a convenient quantitative index of the degree of severity of the illness and was useful for measuring the clinical changes taking place during the trial.

(b) *Physicians' gradings of improvement.* Physicians also made a global assessment of the patients' clinical state on the basis of clinical examination and from information given in nurses' reports.

The following were the grades used:

		Weight
Grade 1	Complete relief of symptoms and signs ..	+3
Grade 2	Marked improvement	+2
Grade 3	Moderate improvement	+1
Grade 4	Slight or no improvement	0
Grade 5	Slightly worse	−1
Grade 6	Moderately worse	−2
Grade 7	Markedly worse	−3

The device of applying a weight to each grade permits any improvement occurring with inert tablets to be taken into account thus giving a more accurate assessment of the pharmacological effects of the drug. For example, if a patient showed moderate improvement (Grade 3 = +1) with inert tablets and a marked improvement (Grade 2 = +2) with phenelzine the improvement accorded to the latter is given by the difference in weights of the respective grades, i.e. +1.

The physicians' ratings and gradings made at the end of the 3rd and 6th weeks were the ones used for statistical comparison, as a pilot study showed that most patients who responded to the drug usually did so by the end of the third

week. This procedure also has the advantage of obviating errors due to the "carry over" effect of the active drug into an ensuing inert tablets period.

7. *Statistical methods.* As pointed out by Rees and Benaim (1960) non-parametric statistics are sometimes more appropriate and, in some respects, more advantageous than the usual parametric methods for use with gradings and ratings.

The principal method used in this study was the Wilcoxon Matched Pairs Signed Ranks Test (Siegel, 1956).

Results

The 21 patients who started in the triple-blind trial comprised twenty women and one man. The age of the group ranged from 31 to 74 years with a mean of 53 years. One patient had to be withdrawn because she developed jaundice during the initial three-week period as discussed later.

Twelve patients had previous attacks of depression, three having had 3 attacks, three 2 attacks and seven 1 attack. All but one of the 22 previous attacks of depression had responded satisfactorily to electroplexy.

The duration of the present illness ranged from 3 weeks to 104 weeks with a median of 10 weeks.

The depressive illness was predominantly endogenous in type in 13, predominantly reactive (or neurotic) in 4, and in 3 patients both endogenous and reactive factors played an important role.

Comparison of Effects of Phenelzine with Those of Inert Tablets

The clinical grades made at the end of the two three-weekly periods are shown in Tables II and III.

Table II

Grade	Weighting	Inert Tablets %		Phenelzine %	
1 Complete symptomatic recovery	+3	5	15	25	50
2 Marked improvement	+2	10		25	
3 Moderate improvement	+1	20		20	
4 Slight or no improvement ..	0	45		25	
5 Slightly worse	−1	15		0	
6 Moderately worse	−2	5		5	
7 Markedly worse	−3	0		0	

Table III

Main Factors in Illness	N	Full Symptomatic Relief %	Marked Improvement %	Moderate Improvement %	Total All Grades of Improvement %	Total Recovery Marked Improvement Only %
Predominantly endogenous ..	13	23	30	8	61	53
Both endogenous and reactive factors important	3	33	0	66	99	33
Predominantly reactive	4	25	25	25	75	50
Totals for group ..	20	25	25	20	70	50

TABLE IV

Results of a Trial with Phenelzine in Depressive Illnesses in a Series of 32 Out-Patients (Uncontrolled)

Main Factors in Illness	N	Total Symptomatic Relief %	Marked Improvement %	Moderate Improvement %	Slight or No Improvement %	Totals %
Predominantly endogenous ..	10	40	20	20	20	100
Both endogenous and reactive factors important	10	20	20	0	60	100
Predominantly reactive	12	50	16	33	0	100
Totals	32	37·5	18·75	18·75	25	100

Phenelzine has a higher proportion of patients showing complete recovery and marked improvement combined (50 per cent.) than inert tablets (15 per cent.). This difference is statistically significant at a confidence level of between 5 per cent. and 1 per cent. The sum of all improvement grades is also statistically significantly greater with phenelzine (70 per cent.) than with inert tablets (35 per cent.) ($P=>0·5$).

The device of applying weights to the physicians' grades enables a more refined assessment of the effects of the drug in the individual patient. Two patients improved to the same extent with inert as with active tablets. Eleven patients improved more with phenelzine than with inert tablets, the sum of weight differences in favour of phenelzine was 22. Three patients improved more with inert tablets than with phenelzine, the sum of difference in weights in favour of inert tablets was 4.

EFFECTS ON VARIOUS SYMPTOMS AND CLINICAL FEATURES

Ratings of various clinical features made before the start of the trial were used for comparison with those made at the end of the three weeks medication with active and inert tablets respectively.

Significantly greater improvement with phenelzine over pre-trial ratings occurred in the following:

	P
Depression	$>·01$
Anxiety	$>·01$
Tension	$>·01$
Agitation	$>·01$
Guilt feelings and self depreciation	$>·05$

Significant improvement occurred with inert tablets compared with pre-trial ratings in the following:

	P
Depression	$<·01$
Tension	$<·01$

Comparison of ratings obtained with phenelzine at the end of 3 weeks with those at the end of three weeks with inert tablets, revealed significantly statistically greater improvement in rating of depression with phenelzine ($P=>\cdot05$).

Using the sum of ratings of individual clinical features as a convenient index of severity of illness it was found that inert tablets showed no significant improvement over pre-trial scores whereas phenelzine showed a statistically higher significant improvement ($P=>\cdot005$). Phenelzine also showed statistically significantly greater improvement than inert tablets ($P=>\cdot01$).

Relapse After Improvement with Phenelzine During the Trial Period

The method of random allocation of active and inert tablets actually resulted in 13 patients receiving phenelzine and seven inert tablets during the initial 3-week period. Of the thirteen patients initially receiving phenelzine, six having achieved some improvement relapsed on inert tablets during the second three-week period.

This finding provides additional evidence that clinical improvement occurring with phenelzine in these patients can reasonably be attributed to the drug's pharmacological actions and not to extraneous factors.

Side-Effects

No instance of jaundice or liver damage occurred with phenelzine. One patient who developed jaundice in the first week of the initial part of the trial and was excluded was found to have been receiving inert tablets only.

Side-effects occurred in five patients, two had oedema of the ankles, two hypotensive symptoms, viz., syncope and postural dizziness. Another patient had marked increase in anxiety, guilt feelings and insomnia. Among these five patients the following additional side-effects also occurred; somnolence, blurring of vision, unsteady gait and tingling sensations in arms.

Comparison of Effects of Phenelzine with Electroplexy

Only three of the twenty patients improved sufficiently with the drug to be discharged from hospital. Two of these patients had received E.C.T. earlier in the illness without benefit.

Five patients who improved with phenelzine but not with inert tablets had to have electroplexy, with recovery. Two other patients slightly improved both with phenelzine and with inert tablets but had to have electroplexy, which resulted in rapid and full recovery. Another six patients who improved neither with phenelzine nor inert tablets had to have E.C.T., which similarly produced rapid and full recovery.

These findings unequivocally demonstrate that phenelzine is not as effective as electroplexy for treating severe depressive states.

Discussion

The results of our double-blind trial show that phenelzine is therapeutically effective in depressive illnesses. Although producing improvement in 70 per cent. and to a greater degree than inert tablets in 55 per cent., thirteen patients still needed to have electro-convulsive therapy to effect a complete recovery. There can be no doubt that the drug is not as effective as E.C.T. for severe depressive illnesses. On the other hand two patients made a good therapeutic response with phenelzine, having failed to benefit from E.C.T. earlier in the

present illness. As pointed out by Rees (1960) there is an urgent need for research to discover the relevant attributes in the individual, whether these prove to be physiological, chemical, psychological or constitutional in nature, to enable a more reliable selection of patients for specific pharmacotherapeutic agents.

It is possible that phenelzine is more effective in depressive illnesses of moderate or mild degree of severity than in the severe forms. It is of interest therefore to compare the results obtained in our group of severe depressive illnesses with a group of 32 less severe depressive illnesses shown in Table IV.

The percentage showing total recovery is greater particularly in reactive depressions. Both endogenous and reactive depressions improved, the latter as in the double-blind trial (Table III) showing the higher incidence of improvement.

Seventy-five per cent. of the group showed recovery, marked or moderate improvement, which is somewhat better than the results in the double-blind trial.

It should be borne in mind that the differences in the out-patient group and the in-patient group were not only in severity but also duration of treatment, which was longer in the out-patient group, and that the manifold sources of error already discussed may, to an unknown extent, have contributed to the slightly higher improvement rate.

In conclusion, the results of the controlled study indicate that phenelzine is therapeutically effective in some depressive illnesses and further research is needed to enable more reliable selection of depressive patients likely to respond to the drug.

References

Benaim, S., and Dixon, M. F., *Brit. Med. J.*, 1958, *ii*, 1068.
De Verteuil, R. L., and Lehmann, H. E., *Canad. Med. Ass. J.*, 1958, **78**, 131.
Dickel, H. A., Dixon, H. H., and Shanklin, J. G., *Clin. Med.*, 1959, **6**, 1579.
Dunlop, E., *R.I. Med. J.*, 1959, **42**, 656.
Fisher, J. D., and Oliver, M. F., *Brit. Med. J.*, 1958, *ii*, 1225.
Frantz, J., *Amer. Med. Ass.*, 1958, **167**, 987.
Furst, W., *Amer. J. Psychiat.*, 1959, **116**, 429.
Hutchinson, J. T., and Smedberg, D., *J. Ment. Sci.*, 1960, **106**, 704.
King, P. D., *Amer. J. Psychiat.*, 1959, **116**, 64.
Rees, L., *Nature*, 1960, **186**, 114.
Idem and Benaim, S., *J. Ment. Sci.*, 1960, **106**, 193.
Sainz, A., *Ann. N.Y. Acad. Sci.*, 1959, **80**, 780.
Sarwen-Foner, G. J., Koryani, E. K., Mezaros, A., and Grauer, H., *Canad. Med. Ass. J.*, 1959, **81**, 991.
Saunders, J. C., Roukema, R. W., Kline, N. S., and Bailey, S. d'A., *Amer. J. Psychiat.*, 1959, **116**, 71.
Seigel, S., *Non-Parametric Statistics*, 1956. New York: McGraw Hill.
Shay, H., and Sun, D., *Ann. Int. Med.*, 1958, **49**, 1246.
Smarr, E. R., Wolf, H., and Pressman, D., *Amer. J. Psychiat.*, 1958, **114**, 1115.
Thal, N. L., *Dis. Nerv. Syst.*, 1959, **22**, 197.
Weiss, L. B., Davidson, J. H., Winsten, S., and Brody, H. J., *Albert Einstein Med. Centre*, 1958, **61**, 229.
Zetzel, L., and Kaplan, H., *New England J. Med.*, 1958, **258**, 1209.

CONTROLLED CLINICAL TRIAL OF ISOCARBOXAZID ("MARPLAN") IN HOSPITAL PSYCHIATRY

By

VASANT G. JOSHI, M.B., D.P.M.*

St. Francis Hospital, Haywards Heath, Sussex

Introduction

A number of synthetic drugs have recently been introduced as specific antidepressants in psychiatry. Isocarboxazid (Marplan) is an analogue of iproniazid (Marsilid). Both belong to the monoamine oxidase inhibitor group of antidepressants. Isocarboxazid is said to be less toxic but of equal potency for a lesser dose than iproniazid. A controlled clinical trial of isocarboxazid was therefore undertaken to assess this drug in the treatment of depression. The results of this trial are reported in this paper together with the results of an uncontrolled trial in a further group of patients (group M) who received isocarboxazid only.

Selection of Patients and Diagnostic Criteria

Clinical psychiatry recognizes two types of depressions: the "Primary" group, further subdivided into endogenous, senile, and agitated, and the "Secondary" or "Reactive" group. The chief distinction between the two groups is that in the latter, a definite cause or causes for the depression in the individual's environment are discernible with relative ease.

In this secondary group an important sub-group of depressions due to long-term institutionalization ought to be emphasized. The depression can be said to be present in many chronic patients in hospital, as a result of many months or years spent in this environment.

The principal object of this trial was to assess the usefulness of isocarboxazid as an antidepressant in the last-mentioned type as well as in the more obvious endogenous and reactive groups of depressions.

Method

A preliminary pilot study with isocarboxazid was made on five patients for one month on a constant dose of one tablet (10 mg.) three times daily. The results were encouraging and it was felt that a double-blind controlled trial should be arranged.

Two statistically comparable groups R1 and R2, as shown in Tables I and II, were arranged from previously selected depressed chronic patients and from new admissions. Two identical batches of special tablets were made, one containing Marplan and the other an inert placebo. The hospital pharmacist dispensed tablets from one batch to group R1 and from the other batch to group R2, but neither he nor the author, staff or patients knew the nature of the tablets until the trial was completed.

* Present address: 153C Matunga, Bombay 19, India.

TABLE I

Groups R1 and R2 by age and sex

	Number of Patients			Age in Years	
	Total	Male	Female	Mean	Standard Deviation
R1	27	10	17	62·9	±11·1
R2	26	9	17	63·7	±10·3

TABLE II

Groups R1 and R2 by diagnostic categories

Group		R1	R2
Primary Depressions	Unclassified ..	5	4
Secondary Depressions related to	Schizophrenia ..	14	15
	Manic-depressive psychosis ..	3	1
	Organic psychosis	2	4
	Mental defect ..	2	1
	Psychopathy ..	1	1
Total Cases		27	26

DOSAGE, OTHER DRUGS, ETC.

Every patient received one tablet (10 mg.) three times daily for 3 months; in addition Becosym Forte 2 tablets once daily and a night sedative, usually sodium amylobarbitone gr. 3 p.r.n., were given. All other medications, physical treatments, etc., were discontinued throughout (except where specifically mentioned—*vide infra*).

RECORDS

All patients were well known to the author before commencement of the trial, and twice weekly assessment of every patient was made. This included interview for subjective and objective appraisal and a special report by the sister or staff nurse in charge of the ward. Particular attention was given to side-effects. Results were charted on specially made forms on the following scale:

marked improvement→ improvement→ no change ←worse ←markedly worse

The same form included a daily temperature, pulse, respiration and sleep record and a once weekly weight record.

The largest group of 41 patients as shown in Table III were given the

TABLE III

Group "M" by sex, age and diagnostic categories

Sex Incidence	Males	6
	Females	35
Age in Years	Mean	56·1
	Standard Deviation ..	±11·3
Primary Depressions	Senile	10
	Endogenous	12
	Agitated	3
Secondary Depressions related to	Schizophrenia	9
	Manic Depressive Psychosis	1
	Organic Psychosis	3
	Mental Defect	—
	Psychopathy	1
	Obsessive Comp. Psychosis	1
	Huntington's Chorea ..	1
Total Cases		41

standard preparation of isocarboxazid. This group also includes the first five patients from the pilot study. It is mainly made up of newly admitted severe primary depressives who would have had to have immediate antidepressant treatment such as drugs, E.C.T., etc. It also includes 16 secondary or institutionalized depressives. Except for the patients in the pilot study this group began their treatment with isocarboxazid about a month later than R1 and R2 groups.

Results

A summary of the results in both the blind trial group "R1" and "R2" and in the uncontrolled group "M" is shown in Table IV. On opening the sealed code at the end of the trial it was found that R1 group had received the dummy tablets and R2 Marplan tablets. For the purpose of statistical analysis both degrees of improvement were counted as success and "no change", "worse" and "changed to other treatment" categories were considered failures. A χ^2 test was performed and gave a result of 7·74, which, for one degree of freedom, is associated with a probability of $P = <0{\cdot}01$. The results of the cases treated with isocarboxazid are therefore significantly better than those of the control group.

Table IV

Results of all groups. The right-hand column shows patients changed to known Marplan tablets or given E.C.T. due to the severity of their condition persisting after 4 weeks or more on the unknown trial tablets

Group	Markedly Improved	Improved	No Change	Worse	Changed Treatment	Total
R1 (Placebo)	—	3	16	—	8	27
R2 (Marplan)	8	5	9	2	2	26
M	7	19	12	3	—	41

Group "M" gave similar results but with a rather higher success rate, 63·4 per cent., compared with 50 per cent. success in the blind trial group R2. This is to be expected because of the uncontrolled nature of this part of the trial. Of the seven cases that improved markedly, two were agitated depressions, two senile depressions, one endogenous depression, one depression secondary to organic psychiatric disease and one depression associated with Huntington's Chorea. The moderately improved group consisted of seven endogenous depressions, six senile depressions, four schizophrenic cases with depression, one agitated depression and one obsessive-compulsive psychosis with depression. The three cases which became worse on treatment were one manic-depressive psychosis, one arteriosclerotic dementia and one endogenous depression.

Side-Effects and Toxicity

(1) *Very severe effects necessitating immediate stoppage of drug.* One 60-year-old chronic schizophrenic with a remote past history of albuminuria but otherwise in good health with normal urine, blood urea and B.P. at the time had an attack of haematuria which cleared after withdrawal of the drug.

A senile dement became grossly confused, especially at night, and had frequent falls; another senile arteriosclerotic fell very frequently despite a

clear sensorium. He was hypertensive and his falls may have been related to vascular or hypotensive effects of the drug.

One patient from group R2 had very severe nasal congestion which subsided only after stopping the drug.

(2) *Other side-effects.* twelve patients complained of coryza-like symptoms with nasal congestion, tachycardia, etc. In three patients it was severe enough to require an antihistamine (Thephorin 1 tab. b.d.). Bilateral pitting oedema was seen in four patients during the second and third weeks and appeared to be related to weight gain.

Tachycardia, weight gain, or slight pyrexia to 98·8°–99·2°F., was noted in eight patients. Before the trial they were grossly retarded vegetative psychotics with asthenia, bradycardia and low body temperature.

(3) *Some interesting side-effects.* Two paraphrenics made better improvement on a combination of isocarboxazid and chlorpromazine (50 to 100 mg. t.d.s.) than on isocarboxazid alone.

Two severely depressed agitated patients who showed little response on isocarboxazid alone, made a dramatic recovery when isocarboxazid was followed within two weeks by two or three E.C.T.s, whereas in their previous depressive attacks, they had required up to four weeks of shock therapy at three E.C.T.s per week.

An inadequate psychopath previously addicted to amphetamine spontaneously reported loss of craving for drugs without exacerbation of anxiety or depressive moods while on Marplan.

A young recurrent depressive who redeveloped active pulmonary tuberculosis was successfully treated for both depression and tuberculosis with isocarboxazid and P.A.S.

Conclusions and Summary

In a strictly controlled trial, isocarboxazid (Marplan) appears to be a useful drug for the treatment of depressions in general.

Secondary depressions in elderly patients in whom features of agitation are marked, respond extremely well.

Psychoneurotic depressions superimposed on an obsessional compulsive neurosis, and depressions with anxiety, all of a younger age group, and probably in females with an asthenic or dysplastic diathesis, may be helped also.

Classic endogenous depression of considerable severity and recurrent depressions of a similar nature are not helped by Marplan.

Minor side-effects clinically resembling those of reserpine but less frequent, appear at the commencement of treatment, and eventually lessen, unlike those produced by reserpine. In a case of active pulmonary tuberculosis, isocarboxazid was successfully used in combination with P.A.S.

Acknowledgments

Grateful acknowledgments are due to Dr. S. G. Bayliss, M.B., B.Chir., Department of Clinical Research, Roche Products Ltd., for generous supplies of Marplan, Becosym, etc., for ready assistance and helpful advice.

My wife, Dr. Kamal Joshi, for much helpful criticism.

Dr. D. W. Liddell, the Physician Superintendent of St. Francis Hospital, Haywards Heath, for permission to carry out the trial.

Mr. Fecit, hospital pharmacist, for arranging dispensing, etc., for the controlled trial.

Sisters, charge nurses, staff and patients for their ready co-operation.

References

1. Azima *et al.*, *Amer. J. Psychiat.*, 1959, **116,** (5), 453.
2. Ayd, Frank J., Jr., *Annal. N.Y. Acad. Sci.*, 1959, **80,** (3), 734–744.
3. University of Cambridge, "Symposium on Depression (1959) Preliminary Report."
4. Barton, Russell, *Institutional Neurosis*, 1959. Bristol: John Wright.
5. McGill University, Conference on Depression, *Canad. Psychiat. Assn. Jl.*, 1959, **4** (Special Supplement).

A CONTROLLED STUDY OF THE EFFECTIVENESS OF NIALAMIDE* ("NIAMID") IN SCHIZOPHRENIA

By

J. G. HEGARTY

A. R. DABBS

and

R. T. ST. BLAIZE-MOLONY

Oakwood Hospital, Maidstone, Kent

Nialamide is claimed to inhibit the activity of the enzyme monoamine oxidase which is known to be responsible for the breakdown by catalytic oxidation of various amines, e.g. serotonin and norepinephrine. It has been suggested that depression may be associated with inadequate levels of serotonin and/or norepinephrine and that the administration of a monoamine oxidase inhibitor should rationally help to relieve depression. No serious side-effects have been reported in the available literature except that agitated patients might become somewhat more agitated and overactive.

It has been suggested by several authors that certain forms of schizophrenia, particularly those characterized by anergy and lethargy, are favourably influenced by the administration of monoamine oxidase inhibitors (1, 2). This study was designed to evaluate as objectively as possible the "psychic-energizing" properties claimed for nialamide on a population of withdrawn, detached and apathetic schizophrenic patients.

It has also been postulated that schizophrenia is in some way related to fluctuations in serotonin and norepinephrine levels (3). It might be expected that drug-induced changes in serotonin level would be reflected as changes in the general schizophrenic condition.

Population

Forty schizophrenic patients, twenty male and twenty female, were selected as subjects for this study. All the patients had been in the hospital for a minimum of ten years and had failed to respond to any form of treatment. All the patients chosen were markedly lethargic, detached, anergic and apathetic. They were those patients who were not a source of trouble on the ward but who required nursing supervision and who led a very routine existence. The majority took part in occupational therapy but their tasks were extremely simple and it was very difficult to induce them to attempt anything at all requiring a degree of concentration and attention. Many of the patients were mute and withdrawn but none were aggressive or overtly hostile.

* "Niamid" brand of Nialamide—1-(2′-(benzylcarbamyl) ethyl) 2-iso-nicotinoyl hydrazine. Tablets kindly supplied by Harvey Pharmaceuticals, Pfizer Ltd.

Method

The patients were randomly divided into two groups, ten males and ten females in each group. All the patients were then interviewed by two psychiatrists and rated on a scale concerned with Ward Behaviour and Psychiatric Symptoms. The Charge Nurse/Sister of the ward assisted in the ratings and the double-blind trial then commenced. One month later the patients were interviewed again and re-rated by the same psychiatrists who were unaware to which group the patient belonged. Following this rating the dosage was increased and three months later the whole assessment procedure was repeated.

Throughout the course of the trial a record was kept of each patient's body weight. Twice weekly blood pressure readings were also taken and weekly white cell counts were carried out.

Dosage

The patients had been divided into two groups by the psychologist and the groups labelled "A" and "B". The hospital pharmacist was provided with a list of patients in their respective groups and he dispensed "A" tablets to the "A" group and *vice versa*. The tablets were outwardly identical but in fact the "A" tablets were inert, and the "B" tablets contained the drug.

The initial dosage for the drug group was 50 mg. t.d.s. (i.e. all patients received 2 tablets t.d.s.). At the end of a month the dosage was doubled and the trial continued for a further three months.

Rating Scale

The scale used was a simplified version of the Hamilton, Smith *et al.* adaptation of the Lorr Scale (4, 5). It consisted of eight items concerned with Ward Behaviour (six from the Nurse's Rating Scale by Lorr plus Hostility/Aggression and Initiative) and seven items concerned more directly with Psychiatric Symptoms (items P1, P4, P8, P11, P13, N17, of the Lorr Scale plus an item relating to the incidence of delusional ideas). All the items could be rated on a five-point scale; high scores were bad and low scores tended toward normality.

This scale was completed for each patient at the outset and repeated after one month and again three months later. After each rating the Scales were given to the psychologist and the psychiatrists had no access to them for future ratings.

Results

No significant improvement in score was demonstrated by the treated group as compared with the control group during the course of the trial. However, it was interesting to note that both groups revealed a consistent overall improvement at each rating though this trend only reached a satisfactory level of significance (beyond the 1 per cent. level) for the group as a whole at the final assessment. The changes noted in both groups at the end of the first month, although in a favourable direction, did not attain significance.

An examination of those items concerned with Ward Behaviour (these ratings had been made with the assistance of the nursing staff) showed that at repeated assessments both groups improved but only the improvement in the drug group approached statistical significance.

The apparent improvement in all the patients during the course of the trial was largely due to the improved ratings of Psychiatric Symptoms. This part of the scale showed that the control group improved significantly (at the 5 per cent. level) while the drug group also improved but not at such a high level of significance.

Physical Measures and Side-Effects

Detailed nursing observation was maintained throughout the trial and a close watch was kept for the appearance of side-effects. No consistent changes in body weight were evident during the trial nor was there any apparent difference between the groups with regard to blood pressure measurements. No changes in the white cell count were obvious during the trial. One female patient who was receiving the active substance developed a transient jaundice within the first month of the study; this subsided when the drug was withdrawn. The tablets were again administered after a month without any subsequent ill-effects.

Four patients who had previously been "bed-wetters" became "dry" during the trial. However, it was discovered at the close that two of these patients had been receiving inert tablets and no conclusions could therefore be drawn.

No patients showed any evidence of increased restlessness, hostility or over-activity, nor was there any evidence of the incidence of those side-effects reported in the literature (6), e.g. dry mouth, sweating, dizziness, constipation, blurred vision, etc.

Discussion

Forty anergic and withdrawn schizophrenic patients, twenty male and twenty female, were divided randomly into two equal groups. A double-blind trial, lasting four months, was carried out using Nialamide and a placebo. No significant improvement could be demonstrated in the treated group compared with the controls. The use of monoamine oxidase inhibitors with this type of patient would not seem to be of value. To quote Regnier, Good *et al.* (7) "the psychiatrist who hopes to see chronic schizophrenics blossom into healthy socially orientated responsiveness will be disappointed by these results". However, the fact that Nialamide did not adversely affect the schizophrenic patients in this trial would indicate that the administration of this drug would not be precluded in mixed schizophrenic/depressive conditions.

This trial revealed that all the patients did benefit to some extent and this could best be accounted for by the response of the patient to the greater interest shown by both psychiatrists and nurses during the course of the study.

Acknowledgments

We wish to thank Dr. R. G. McLaren, Medical Superintendent of Oakwood Hospital, for making available the facilities which made this study possible. We also wish to express our thanks to Mr. J. Sim, Pharmacist, for his help in organizing this trial and to the Medical and Nursing Staff for their co-operation.

References

1. Davies, T. S., Paper read at International "Niamid" Symposium, Lisbon, 1959.
2. Feldman, P. E., *Dis. Nerv. Syst.*, **20**/8, 41–49.
3. Heath, R. G., Leach, B. E., Byers, L. W., *et al.*, *Amer. J. Psychiat.*, **114**/8, 683–689.
4. Lorr, M., "Multidimensional Scale for Rating Psychiatric Patients", Hospital Form. *Vet. Admin. Tech. Bull.*, 1953, TB. 10–507.
5. Hamilton, M., Smith, A. L. G., Lapidus, H. E., and Cadogan, E. P., *J. Ment. Sci.*, 1960, **106**/442, 40.
6. Ayd, F. J., Bianco, E., and Zullo, L., *Dis. Nerv. Syst.*, **20**/8, 34–40.
7. Guertin, W. H., Regnier, W. O., Good, R. W., and Nicholson, G., *ibid.*, 1960, **21**/6.

A CONTROLLED TRIAL OF METHAMINODIAZEPOXIDE (CHLORDIAZEPOXIDE, "LIBRIUM") IN THE TREATMENT OF ANXIETY IN NEUROTIC PATIENTS

By

F. A. JENNER, M.B., Ch.B., Ph.D., D.P.M.

Lecturer in Psychiatry

R. J. KERRY, L.R.C.P., M.R.C.S., D.P.M.

Senior Registrar

and

D. PARKIN, M.B., Ch.B., D.P.M.

Registrar

Department of Psychiatry, The United Sheffield Hospitals and the University of Sheffield

In the absence of full understanding of the nature of anxiety neurosis, therapy must be, in part, symptomatic. Along with reassurance and efforts to comprehend the important aspects of the situation, most doctors are forced to use tranquillizing drugs. Careful clinical studies are, therefore, important.

This study is designed to investigate whether or not methaminodiazepoxide (Librium—Roche Products Ltd.) is effective in affording relief from anxiety in neurotic patients. Chemically it is 7-chloro-2-methylamino-5-phenyl-3H-1, 4-benzodiazepine 4-oxide hydrochloride. It is structurally unrelated to any other tranquillizer and if active is of special pharmacological interest. Randall *et al.* (1960) have described some of the pharmacological properties of methaminodiazepoxide. In animals it is of low toxicity, it produces a taming effect on vicious monkeys and stimulates appetite and weight gain in various animals. It has only slight hypnotic properties but it is a muscle relaxant and gives rise to ataxia in sufficiently high doses. The site and mode of action are unknown. Bernsohn *et al.* (1960) have shown that very large intraperitoneal doses (25 mg./kg.) increase the level of cerebral adenine triphosphate and reduce cerebral creatinine phosphate in rats. Further fundamental studies are required but the clinical interest in methaminodiazepoxide is based upon claims made for its therapeutic effects. The reports are from various parts of

America and the continent; they include Harris (1960) and Voelkel (1960) both of whom emphasize its value in anxious and agitated states.

The first but uncontrolled American studies make considerable claims for its effectiveness in relieving anxiety in neurotic subjects, and fourteen papers on various aspects of its use and pharmacology appear in Supplement 3, *Diseases of the Nervous System*, Volume 21 (1960). Only two controlled studies have come to our notice. Close *et al.* (1960) have made a double-blind study of fourteen patients with "severe, chronic disabling agitation", but various diagnoses. Their results confirm that methaminodiazepoxide helps such people; the diagnoses did not seem important. Rickels (1960) has compared, under controlled conditions, methaminodiazepoxide with several other tranquillizers. He studied non-psychotic out-patients but the results were presented in a preliminary report which is not yet available to us.

Methods

This controlled study was carried out on out-patients. A preliminary and uncontrolled assessment of the safety and dosage of the drug was performed on day-patients and in-patients. This pilot study suggested, in agreement with earlier workers, that a suitable dosage lay between 10 and 50 mg. three times a day. Twenty milligrammes (i.e. 2 capsules) were given three times daily to each patient. The study was arranged to compare the effects of this dose of methaminodiazepoxide with the effects of 2 capsules of lactose three times a day. The capsules were prepared to appear identical by the manufacturers—Roche Products. The packing, labelling and dispensing were arranged so that a patient received two weeks supply of one, followed by two weeks supply of the other, capsules. The code indicating when the patient received methaminodiazepoxide was known only to the packer of the bottles. The two preparations could have been distinguished only if the capsules were opened as methaminodiazepoxide is bitter. Each patient was told he was to receive a new drug which was likely to help him. He was asked to co-operate in the assessment of its value to him.

The patients were seen, if possible, at weekly intervals during the trial period. Gross fear of travelling, also personal reasons, necessitated seeing some patients at fortnightly intervals. At the conclusion of the four weeks of the controlled assessment, 10 mg. of methaminodiazepoxide was given three times a day to patients who had done well during some part of the trial. The code had not at that stage been broken.

The patients included those newly referred by their general practitioners and out-patients who had attended our clinics for periods of up to three years. The latter group was well known to us. In all cases neurotic anxiety was a prominent symptom. They had been diagnosed as anxiety neurotics. Some of them showed obsessional and some hysterical features. No attempt was made to select patients for sex and age. They were in fact consecutive cases in the out-patient department. Typical symptoms were fear of travelling, being alone, collapsing in the street, shopping, being in a crowd, talking to other people and claustrophobia. Such fears ranged from the intense phobias of things which were avoided at all cost to difficulties which were faced but which gave rise to the autonomic effects of anxiety including tachycardia, frequency of micturition, nausea, diarrhoea, etc.

The patients were all given supportive psychotherapy in brief interviews with an emphasis on reassurance. Some of the patients had previously had group or more intensive individual psychotherapy but without material benefit. Most patients had also at some time previously had other tranquillizers. The patients were advised not to take any other drugs during the trial period. A few, however, reacted with anxiety to the advice to discontinue nightly sedatives which they had been taking for a long time. They were allowed to continue with these. Twelve patients were also attending weekly groups for psychotherapy.

Five visits were made at weekly intervals during the trial. At each of these the patient's progress was recorded on a printed form by the doctor. This gave details of the duration and severity of the symptoms. The relevant rating was underlined and on each occasion it was indicated whether the patient felt he was improving or deteriorating. The essential details of the form are presented in Table I. Space was left for further comments and routine clinical notes were also kept in addition to these trial record sheets.

Table I also shows the simple numerical rating which was used to facilitate statistical evaluation of the results. The doctor did not have the previous sheets available to him when he filled in subsequent forms, nor did the patient necessarily see the same doctor on each occasion.

The statistical methods used were all taken from Fisher (1954). Where the differences of means was studied, Student's t test was applied; the results seemed to be normally distributed. In other cases the correlation coefficient was calculated and its significance assessed from the tables given by Fisher.

TABLE I

Librium Trial Record Sheet

DATE:	DOCTOR:	TRIAL NO.:

NAME OF PATIENT:	AGE:	SEX:	HOSP. NO.:

LEADING SYMPTOMS

	Duration	Getting Better or Worse Now
1.		
2.		
3.		

PREVIOUS TREATMENT

Mental Hospital	E.C.T.	Sedatives	Nil.

SYMPTOMS

Anxiety	Incapacitating 6	5	Severe 4	3	Moderate 2	1	Negligible 0
Depression	Incapacitating 6	5	Severe 4	3	Moderate 2	1	Negligible 0
Lack of ability to work	Severe 6	5	Moderate 4	3	Mild 2	1	Absent 0
Initiative	Apathetic 4	3	Disinterested 2	1	Normal 0	−1	Overactive −2
Sexual adjustment	Very unhappy 6	5	Unhappy 4	3	Moderate 2	1	Satisfactory 0
Sleep	Very bad 4	3	Poor 2	1	Normal 0	−1	Excessive −2
Phobias	Incapacitating 6	5	Severe 4	3	Moderate 2	1	Negligible or Absent 0

Nature of Phobia:

Weight:	Appetite: Increased / Average / Poor
	−2 −1 0 1 2

Patient's opinion of progress:

Score for patient's opinion: − Means getting worse; + Means getting better

Rating from −5 to +5

SIDE-EFFECTS

Menstrual	Date of last period	Usual cycle	Days loss	Day cycle
	State any change in cycle during trial:			

Underline the appropriate headings:

Headache	Severe	Moderate	Nil
Giddiness	Severe	Moderate	Nil
Nausea	Severe	Moderate	Nil
Urinary frequency	Severe	Moderate	Nil
Nocturia	Severe	Moderate	Nil
Muscle tenderness	Severe	Moderate	Nil
Muscle spasms	Severe	Moderate	Nil
Cramps	Severe	Moderate	Nil
Ptosis	Severe	Moderate	Nil
Drowsiness	Severe	Moderate	Nil
Ataxia	Severe	Moderate	Nil
Sore throat	Severe	Moderate	Nil
Increased talkativeness	Severe	Moderate	Nil

OTHER COMPLAINTS

RESULTS

Ninety-nine patients were included in the trial but controlled information is only available from ninety-five patients. These ninety-five patients received both the placebo and the active substance. Table II shows the results presented in terms of the patient's opinion as very good, good, poor and bad. This

TABLE II

The Patients' Response to Methaminodiazepoxide Assessed from the Difference in the Ratings of the Patients' Opinion of Methaminodiazepoxide and the Placebo

	Total No. of Patients	Male Patients	Female Patients
Very good	39	21	18
Good	19	8	11
Moderate, No response } Poor	26	5	21
Bad	11	3	8
Totals	95	37	58

classification depended upon the figure obtained by adding assessments of the patient's opinion of his improvement for the two weeks on the active substance and subtracting the assessments made on the two visits when the placebo had been taken. If the value was negative the response was labelled as bad, between 0 to 2 poor, 4 to 6 good and over 6 very good. The values for patients seen fortnightly were doubled for comparative purposes. To obtain a figure of +3

or more for any one assessment, the patient was required to have given a categorical assurance that he had improved. For +5 the patient had to say that the treatment was of exceptional value or that he had not felt so well for a year or more.

The result of the controlled study is a convincing one in favour of the active substance and applying Student's *t* test to these differences between ratings on the active substance and the placebo $p<0{\cdot}001$. An analysis of the figures for the male and female patients shows that the males respond significantly better than the females in terms of our ratings $p<0{\cdot}02$. This response is not due to age differences between the two groups as the correlation coefficients between age and response are not significant for the whole group nor for either sex.

The patients in whom the active drug was felt to have had a bad (eleven) or no effect (seventeen) included two in whom some suspicion of a psychosis arose. In six of the other patients important environmental factors which might have affected the results could be seen. The failures, although included in the totals, were analysed more closely in retrospect than the successes in which environmental factors may also have played a part. Duration of illness and success ratings of methaminodiazepoxide over placebo gave a positive correlation $p<0{\cdot}05$. This may be due to a tendency to overrate improvement in patients whom one has failed to help for some years and also to the lower placebo response in these patients.

The correlation coefficient for each sex between success of therapy and body weight was not significant. The dose to body weight ratio does not seem, therefore, to be very critical. This is confirmed by patients who did well on the trial while taking the active substance. Most of these responded again to methaminodiazepoxide after the trial on half the dose originally used. It was difficult to distinguish their response when they received 10 mg. three times a day from that when they had been receiving 20 mg. three times a day.

As has been stated, ninety-nine patients were at first admitted to the controlled trial. Of these one failed to re-attend and has been excluded as we do not have any information about his response nor his reason for not returning. Nine other patients did not complete the trial, one because of severe ataxia which was probably a genuine side-effect and two following severe hysterical responses to the placebo capsules. One other patient was admitted to another hospital with increasingly severe anxiety during the trial, but is included in our considerations as a very poor response. Two patients had done so well for the first fortnight and relapsed so badly one day after changing to placebo, that they were taken off the trial and given known active capsules without necessitating breaking the code but with beneficial effect. In one of these cases the general practitioner wrote, realizing correctly that the patient's improvement and relapse were to be explained on the basis of the design of the trial. Four patients were taken off the trial when the code was broken for the other patients and when the results showed that it was unjustifiable to continue giving unknown capsules when it was clear that the question posed by the trial had been answered. Only one of these four patients had not at least one week on both types of capsules.

The effect of methaminodiazepoxide appears to be rapid and most patients reported improvement within one to two days of taking the active substance. Of these who relapsed severely when changed over from the active substance to placebo, the relapse also occurred quickly—within three days.

The placebo response in the trial was assessed on the forty-nine patients who received the inactive capsules first. Twenty-four said they felt no change.

Seven patients complained that they were made worse; two were taken off the trial for the apparent side-effects of dimness of vision and feeling faint. One patient had ataxia and the dose was reduced. After the cross-over this patient improved and the full dose of the active substance was given for one week without any further ataxia. The six patients who showed a marked favourable response were all patients who had been referred to the clinic within five weeks of starting the trial. The more regular attenders were less impressed. The percentage placebo response was 36 per cent. which is a common finding in many trials. Eighteen patients said they felt they were being helped and six of these were particularly impressed. Each patient had been reassured as well as being given a full physical examination.

Of the specified symptoms on the trial sheet, the changes correlate so strikingly that less specific information concerning undividual symptoms was obtained than had been anticipated. When a patient felt well all his symptoms improved. It was found that it was impossible either to assess or compare sexual adjustment because through differences in mental status, environment and language complexities, standards could not be set. Some patients did lose fear of intercourse whilst others seemed to lose libido.

Anxiety which was severe in most patients and the associated milder depressions and insomnias were decreased by methaminodiazepoxide. At the same time the patients' ability to work was increased, as was their initiative and interest in other affairs. In this trial there was no significant increase in weight or appetite. This has also been reported by Harris (1960), Voelkel (1960) and others. The patients' weights varied as they were all weighed fully clothed but no persistent trend was discernible.

The patients receiving group psycho-therapy guessed the design of the trial after the change-over; some who had been doing well did badly and vice versa. The two groups were very impressed and especially by the ability of some of their members to take an active part in the group for the first time.

The patients who appeared to respond best were those with phobias or those complaining of unpleasant somatic disturbances. The more hysterical the symptoms the worse the response. Obsessional checking was relieved in some patients and in two who had been followed up for over two years. The results when treated separately for each observer led to the same conclusions.

Side-Effects

Few side-effects of the drug were found. Of these only two—slight drowsiness and ataxia—can be convincingly shown to have been caused by methaminodiazepoxide in this trial. Harmless drowsiness often appeared on the first two to three days. Twenty-three cases complained of definite drowsiness within the first few days which disappeared on continued therapy. There was no correlation between the incidence of drowsiness in either sex with the age of the patient.

Subjective ataxia occurred more frequently in the elderly. Only eight cases reported the symptom while taking methaminodiazepoxide and two complained while taking the placebo. The youngest patient was thirty-nine and three were over sixty, whilst the average age of the patients under trial was 37·2 years. The dosage was reduced in two cases from 20 mg. to 10 mg. three times a day and the ataxia became less severe. One patient refused to continue taking methaminodiazepoxide. In this case and one other the ataxia was objectively discernible.

Of the other items which were listed as possible side-effects (although they were also common symptoms of anxiety neurosis) each item was complained of more frequently by patients receiving the placebo. This was especially true of headaches of which eighteen patients spontaneously complained whilst receiving the dummy and only one whilst receiving methaminodiazepoxide.

Details of menstruation were taken from all the women who were included in the trial and although some were suffering from irregularities, there was no reason to think these were produced or aggravated by methaminodiazepoxide.

One patient complained of haematuria but by the time a specimen was obtained and examined under the microscope no red cells were seen. He continued on the trial without any ill-effects.

Special care was taken to see whether methaminodiazepoxide produced depression. There was no positive evidence. In fact the slight depression complained of by many neurotics was reduced when receiving active therapy. There were no cases of sore throat nor any skin eruptions caused by methaminodiazepoxide in this trial.

Discussion

The trial shows convincingly that methaminodiazepoxide is more effective in relieving anxiety in neurotic patients than a placebo. It only gives controlled information, however, over a period of two weeks treatment. Although it is our impression that this may be the drug of choice for the treatment of anxiety, further controlled trials of methaminodiazepoxide against other tranquillizers, and for longer periods, are necessary. The trial contains the defect that the contents of the two capsules differed in taste. Although it is difficult to believe that this can seriously invalidate our results, we have found, upon subsequent enquiry, that a small minority of patients do in fact open capsules and believe that this is the correct way to take them. It is also to be accepted that patients do not always take medicines and particularly not in the precise way they are prescribed. This, however, would tend to make the result more significant.

It may well be that patients whom one has known a long time are rated differently from new patients; it is also true that such patients included in a blind trial and who improve and relapse at what turns out to be the appropriate times, are very convincing to the observer. This was illustrated by four patients of this series who were able to travel alone for the first time in periods ranging from one to three years. One man who had many treatments including leucotomy over a period of twenty-eight years, reported improvement coinciding with changing from the placebo to the active substance.

It is important to state that we are only studying symptomatic improvements, not cure of anxiety neuroses. Despite this, many patients were able to live far more normal lives and to travel on buses or walk in the street alone without severe discomfort even after prolonged incapacity. It should also be stated that our results only give information about anxiety in certain patients and not anxiety in general.

The drug appears to be safe and if these results are confirmed it could be recommended for use in general practice. These results do not exclude more toxic effects when treatment is prolonged. Other workers, e.g., Harris (1960) have maintained treatment for periods of up to six months without difficulty. The permanence of therapeutic effect, which is beyond the scope of this trial, will require prolonged assessment.

Summary

A double-blind cross-over trial of placebo against methaminodiazepoxide (Librium—Roche Products) has been carried out. The results show that methaminodiazepoxide is an effective agent in the relief of anxiety in neurotic patients. The side-effects and other factors have been discussed.

Acknowledgments

We thank Professor E. Stengel and Dr. W. L. Tonge for their help and advice. All the patients studied were under their care. We are indebted to the nursing staff of the United Sheffield Hospitals for accepting the extra work involved. We are also grateful to Roche Products Limited, especially to Dr. Margaret Lowe and Mr. G. Calder, for providing the materials and advice.

References

Bernsohn, J., Possley, L., and Custod, J. T., "Alterations in Brain Adenine Nucleotides and Creatinine Phosphate *in vivo* after the Administration of Chlorpromazine, JB 516, Dilantin and Ro 5-0690 (Librium)", *Pharmacologist*, 1960, **2**, 67.

Close, J. H., Gogerty, J. H., and Payne, R. W., "Double-blind Evaluation of Methaminodiazepoxide (Librium)", *ibid.*, 1960, **2**, 64.

Fisher, R. A., *Statistical Methods for Research Workers*, 1954. Edinburgh: Oliver and Boyd.

Harris, T. H., "Methaminodiazepoxide", *J. Amer. med. Ass.*, 1960, **172**, 1163.

Randall, L. O., Schallek, Wm., Heise, G. A., Keith, E. F., and Bagdon, R. E., "The Psychosedative Properties of Methaminodiazepoxide", *J. Pharmacol.*, 1960, **129**, 163.

Rickels, K., "A Report on Controlled Evaluations of Several Tranquilizing and Anti-Depressant Agents in Non-Psychotic Out-Patients." Paper read at the 35th Congress of the Pan-American Medical Association. Mexico City. May, 1960.

Voelkel, A., "Erfahrungen mit Librium bei psychomotorischen Unruhe- und Angstzuständen", *Med. experiment.*, 1960, **2**, 170.

A CONTROLLED COMPARISON OF METHAMINODIAZEPOXIDE (CHLORDIAZEPOXIDE, "LIBRIUM") AND AMYLOBARBITONE IN THE TREATMENT OF ANXIETY IN NEUROTIC PATIENTS

By

F. A. JENNER, M.B., Ch.B., Ph.D., D.P.M.
Lecturer in Psychiatry

R. J. KERRY, L.R.C.P., M.R.C.S., D.P.M.
Senior Registrar

and

D. PARKIN, M.B., Ch.B., D.P.M.
Registrar

Department of Psychiatry, The United Sheffield Hospitals and the University of Sheffield

In another paper, Jenner, Kerry and Parkin (1961) confirmed the views of earlier workers, Harris (1960) and Voelkel (1960) and others that methaminodiazepoxide is an effective agent in relieving anxiety in neurotic patients. That study was a blind controlled comparison of methaminodiazepoxide against lactose, but gave no indication of its value as compared with other drugs. The present paper is a comparison of methaminodiazepoxide (Librium, Roche) and amylobarbitone. The latter drug was felt to be one of the best known and most reliable drugs used in psychiatry for the treatment of anxiety. Raymond, Lucas, Beesley, O'Connell and Fraser-Roberts (1957) compared it very favourably with benactyzine, chlorpromazine, meprobamate, sedaltine and lactose. In that trial amylobarbitone was the only drug significantly better than lactose.

Method

The patients selected were the first 92 new or old cases attending the out-patient department suffering from neurotic anxiety. There was no selection for either age or sex. The nature of the trial was explained to each patient and they were asked to co-operate in finding which preparation was most helpful to them. It was decided to arrange the doses so that two capsules were to be taken three times a day throughout the trial. The dosage used was methaminodiazepoxide 20 mg. three times a day, and amylobarbitone 60 mg. (approximately 1 grain) three times a day. On the first visit the patient's condition was assessed and two weeks' supply of one type of capsule was prescribed. The second attendance was made two weeks later, when progress was recorded and two weeks' supply of the other capsules given. All the capsules used were identical in appearance. A third and last visit was made after another two weeks for a final assessment. The order in which the drugs were given was unknown to the doctor and the patient. On each visit the patient's impressions were recorded on a simple questionnaire and any other comments which the doctor felt relevant were written down. The only distinguishing feature between the capsules was their taste if they were opened—although both were bitter, methaminodiazepoxide was more bitter than amylobarbitone.

The patients were all given supportive psychotherapy in brief interviews with an emphasis on reassurance. Some of the patients had previously had group or more intensive individual psychotherapy but without material benefit. Most patients had had and were having other tranquillizers at the time of the initial interview. They were advised not to take any other

drugs during the trial period. A few, however, were disinclined to give up nightly sedatives which they were taking. They were allowed to continue with these.

The questionnaire used to assess each patient's progress is shown in Table I. On the first visit the patient's symptoms were rated as absent, mild or severe. (The figures 0, 1 or 2 were used respectively to indicate this.) On subsequent visits the patient was questioned to indicate whether he had improved, got worse, or remained in the same condition since his last visit. (A minus sign indicated improvement and a plus sign that the symptoms had increased, the figures 0, 1 or 2 were used to indicate the degree of change.) The patient was finally asked to state his overall preference for one or the other of the preparations; this was rated as no preference, slight preference or strong preference. Table II is constructed from the answers given to this question.

TABLE I

Patient..... Dr..... Trial No.....

Age..... Sex..... M.S.W.D. Sep..... Hospital No.....

Diagnosis.....

Leading Symptoms (1) .....

(2) .....

Duration of Illness.....

Most striking features: Obsessional .....

Phobic .....

Hysterical .....

Previous or present treatment and opinion: LIBRIUM .....

BARBITURATES .....

Rating: Initial 0=absent, +1=mild, +2=severe, −1=slight opposite, −2=severe opposite. Follow-up 0=no change, −1=better, −2=much better, +1=worse, +2=much worse.

(this gives the change)

	Initial	2	3	4	5
How are you?	.....	.....	.....	.....	.....
Presenting symptom	.....	.....	.....	.....	.....
Fear (subjective)	.....	.....	.....	.....	.....
Depression	.....	.....	.....	.....	.....
Apathy	.....	.....	.....	.....	.....
Lack of concentration	.....	.....	.....	.....	.....
Irritability	.....	.....	.....	.....	.....
Sleep (rate type of disorder)	.....	.....	.....	.....	.....
Headache	.....	.....	.....	.....	.....
(note characteristic and change)	.....	.....	.....	.....	.....
Anorexia	.....	.....	.....	.....	.....
Ataxia	.....	.....	.....	.....	.....
Other symptoms (specify)	.....	.....	.....	.....	.....
	.....	.....	.....	.....	.....
	.....	.....	.....	.....	.....
	.....	.....	.....	.....	.....

Work 0=satisfactory, 1=with difficulty, 2=losing some time, 3=off work.

Working Ability	House	.....	.....	.....	.....	.....
	Job	.....	.....	.....	.....	.....

For statistical purposes χ^2 was calculated for the significance of the figures for drug preference shown in Table II. Slight preference in that Table was treated as no preference for statistical purposes. It is to be appreciated that the likely value of a drug to a patient depends upon the probability that he will have no preference. This is not taken into account when calculating the statistical significance from χ^2. In Table II a strong preference is reported by 70 per cent. of the patients. In Table III where symptoms are presented separately the number with no preference is of more relevance. In that Table χ^2 and p are presented for a whole series of related symptoms. Despite statistical objections to this the results are striking, but the difficulties of interpreting them are clinical as well as statistical.

Table II

The Table Shows the Numbers of Patients Expressing Strong, Slight or No Preference, for Amylobarbitone or Methaminodiazepoxide. χ^2 for the Strong Preference are as follows: Total 26, Male 13·2 and Female 12·6, all at One Degree of Freedom, are very Highly Significant. The Differences in Male and Female Responses are not Significant

Preference	No. of Patients	Male	Female
Strong preference for *Methaminodiazepoxide*	53	25	28
Slight preference for *Methaminodiazepoxide*	6	2	4
No preference	10	3	7
Slight preference for *Amylobarbitone*	6	3	3
Strong preference for *Amylobarbitone*	12	5	7
No result obtained	5	2	3
Total	92	40	52

Table III

The Table Shows the Number of Patients Suffering from Various Symptoms at the Beginning of the Trial, Their Preferences for One or Other of the Preparations for that Symptom, or Lack of Apparent Side-effect, and Their Statistical Evaluation. A Critical Appraisal of the Possible Interpretation is Made in the Text

Item	No. of Patients Initially Complaining of Symptom	No. Expressing Preference in Respect of the Symptoms and Side-effect for: Amylobarbitone	Methaminodiazepoxide	χ^2	p<
Drowsiness	24	20	27	1·04	0·5
Subjective fear	90	13	52	23·4	0·01
Depression	41	11	23	4·24	0·05
Apathy	28	2	15	9·94	0·01
Concentration	31	6	17	5·28	0·05
Irritability	48	9	28	9·75	0·01
Sleep:	50	9	29	10·55	0·01
Falling asleep	37	8	24	8·00	0·01
Duration of sleep	31	6	17	5·25	0·05
Broken sleep	27	6	8	0·29	0·70
Early waking	20	4	16	7·20	0·01
Headache:	47	9	31	12·10	0·01
Frequency of headache	—	2	17	11·82	0·01
Intensity of headache	—	4	17	8·05	0·01
Duration of headache	—	4	11	3·26	0·10
Difficulties with work	50	6	26	12·50	0·01
Anorexia	24	7	21	7·00	0·01
Ataxia	16	4	10	2·57	0·20
Vomiting	3	3	8	2·27	0·20

Results

The fact that more patients preferred methaminodiazepoxide to amylobarbitone is striking and this is shown in Table II where the preferences are rated as strong, slight or negligible.

As in the previous trial (Jenner *et al.*, 1961) it is difficult to assess the specificity of the drug for various symptoms. If a patient responded to the drug, he tended to show improvement in all his symptoms. It is possibly for this reason that methaminodiazepoxide is apparently preferred by more patients for every symptom. This is shown in Table III. In that Table these results are presented as numbers of patients showing a preference for amylobarbitone, or methaminodiazepoxide for each symptom. Experience with the type of patient treated suggests that patients who have a sense of well-being underestimate their symptoms and side-effects, whilst those who feel ill tend to overestimate them. Other drugs are also sometimes taken, often without the doctor knowing.

From the point of view of the treatment of out-patients it is interesting that the greatest similarity is shown in response to questions about drowsiness. It can be seen in Table III that there is little to choose between the two drugs at these doses if one is concerned about producing drowsiness. This is a particularly undesirable side-effect in drivers, machine workers, etc.

Headache was complained of by 47 patients at the first visit. Of these 44 described them as tense, dull, a feeling of tightness, or indescribable. The other 3 patients described them as throbbing. Thirty-one patients thought methaminodiazepoxide preferable for their headaches, 9 preferred amylobarbitone. Six patients felt that both drugs were equally effective and of definite value.

Eleven were not helped by either drug. Ten patients complained of headache for the first time during the course of the trial—6 whilst receiving amylobarbitone and 4 whilst receiving methaminodiazepoxide. When headache was relieved it was reported to be less frequent, less intense and of shorter duration.

The effect on sleep is assessed for sleep at night as distinct from the side-effect of drowsiness by day. Although the capsules were taken by day, patients had changes in their sleep at night. It should be remembered that some patients continued their customary night sedation (usually a barbiturate) throughout the study. It is not suggested that methaminodiazepoxide is suitable for night sedation when compared with the established drugs (e.g. barbiturates) used for this purpose. Table III shows the number of patients who would choose methaminodiazepoxide or amylobarbitone taken during the day for its effects on their sleep at night. More reported ease in falling asleep, increased duration of sleep, reduction of the number of times sleep was disturbed and loss of early waking on methaminodiazepoxide. A similar consistent improvement in all aspects of sleep was reported by patients who slept better at night on amylobarbitone given during the day.

The symptom of apathy showed that 15 patients preferred methaminodiazepoxide and only 2 amylobarbitone. It is probable that the decreased apathy whilst on methaminodiazepoxide is also reflected in improved working ability.

Severe ataxia did not appear in any patient on methaminodiazepoxide nor was it produced by amylobarbitone. In a previous study severe ataxia was found and seemed to be produced by methaminodiazepoxide. Sixteen patients reported subjective unsteadiness of gait at the first interview classified in Table III as ataxic; of these 10 were improved by methaminodiazepoxide and 4 by amylobarbitone. Our total experience with methaminodiazepoxide by now probably includes over 300 patients. Drowsiness and ataxia are the

important side-effects produced. Severe ataxia is more common in elderly patients, and its absence as a side-effect in this trial may be due to only two patients being over sixty years of age. Looking back on our previous trial we note that some of the younger patients who appeared to have ataxia also had marked hysterical features. In some, this complaint may have been suggested by the doctor discussing this in order to complete the rating scale. The fact that it occurred in two patients whilst they were receiving lactose supports this view. Previous work gave the impression that patients with conversion symptoms did less well. In Table IV an attempt is made to separate some of the patients

TABLE IV

The Numbers of Patients Whom it was felt could be Classified According to Whether They had Obsessional, Hysterical or Phobic Features as the Most Prominent Accompaniment of Their Anxiety, and Their Overall Preferences for the Two Drugs Being Tested

Prominent Features	No. Patients Showing a Preference for: Methamino-diazepoxide Strong	Methamino-diazepoxide Slight	Amylobarbitone Strong	Amylobarbitone Slight	No. with No Preference	Total
Hysterical ..	8	1	1	0	3	13
Phobic	24	4	8	3	4	43
Obsessional ..	13	0	1	0	2	16

into those showing predominantly hysterical, phobic or obsessional features. Hysterical features included aphonias, pains and globus. The phobias included claustrophobia, fear of travelling, fear of crowds, fear of being alone and other morbid fears. Obsessional features included re-checking, hand washing and other repetitive behaviour. The preferences for each drug are given under these headings. The preference for methaminodiazepoxide is marked in each type of patient. The difference in the results for phobic, hysterical and obsessional symptoms is not striking. This result does not confirm our previous impression. It does, however, show that even when the results are split in this way the overall result is the same.

Analysis of the responses in relation to the patient's age shows no significant correlation. The ages varied from 19 years to 63 years and the average age was 37 years (38 years for females and 36 years for males). Most of the patients were between the ages of 20 and 50 years.

The length of time the patient had been ill seemed to have no bearing on the drug preferred. When the sex of the patient was considered, males showed a slightly but not statistically significant, greater preference for methamino-diazepoxide than females (see Table II). This differs from the more significant results in the previous trial (Jenner *et al.*, 1961).

The present trial included 49 people who had previously received methaminodiazepoxide, of whom 31 had given a report favourable to this drug. The possibility that we had selected people who respond favourably to methaminodiazepoxide has therefore to be considered. As the results from the remaining 43 patients are equally convincing we feel that the conclusions from this trial have not been biased in this way.

One of us (J.) seems to have questioned the patients more closely in regard to vomiting and nausea. He recorded the fact that 7 patients complained

of this only while taking amylobarbitone and one patient only while taking methaminodiazepoxide. Three patients initially complained of vomiting and 2 seemed to have been helped by amylobarbitone and 1 by methaminodiazepoxide. Another one of the authors (P.) recorded one case in which nausea occurred only when the patient was taking amylobarbitone. Nausea and vomiting in neurotics taking barbiturates is also reported by Goodman and Gilman (1955).

Discussion

The results suggest that methaminodiazepoxide is likely to be superior to amylobarbitone for the symptomatic relief in a neurotic patient. It is possible that the dose of methaminodiazepoxide used in this study was too high and that of amylobarbitone too low for a fair comparison. Our impression from uncontrolled studies is that 10 mg. three times a day of methaminodiazepoxide is adequate and little is gained from higher doses. Larger doses of amylobarbitone would, however, be more effective but always at the price of increasing drowsiness. Raymond *et al.* (1957) used 100 mg. of amylobarbitone three times a day, but they do not discuss the drowsiness this produces. We feel that amylobarbitone would not be as suitable for prolonged treatment as methaminodiazepoxide, even if it were more effective in higher doses. Nevertheless, it can only be concluded from this trial that in the doses used methaminodiazepoxide is more likely to be effective than amylobarbitone.

The safety of methaminodiazepoxide is in its favour, particularly for prolonged out-patient or general practice use. Large doses have been taken without lethal effect. Hines (1960) reports a schizophrenic female aged 47 who took 1,150 mg. methaminodiazepoxide in 20 minutes, and a male patient aged 22 who took 1,600 mg. of methaminodiazepoxide in 24 hours. In neither case was gastric lavage used and no long-term physical impairment caused. In contrast barbiturates are one of the commonest suicidal agents.

One of the major limitations of this trial is the short period of two weeks spent on each drug. Both drugs are, however, fairly quickly effective, especially amylobarbitone. Their relative merits have not been tested over longer periods. Our impression of these drugs in prolonged treatment is that both lose their efficacy in some cases. It is known that barbiturates lead to habituation, but not if this occurs with methaminodiazepoxide. Prolonged trials to decide this and other matters would be difficult, and choice may have to be left to clinical experience. Most clinicians would agree that in acute attacks of anxiety, very high doses of amylobarbitone (or another barbiturate) with the patient in bed is of exceptional value. It is not to be suggested that methaminodiazepoxide in this role is in any way the equal of amylobarbitone. The results in this trial only show the relative values of the two drugs in out-patient practice with anxious patients who are attempting to lead a comparatively normal life. It must be pointed out that the results of any clinical trial are always in question until confirmed by similar studies in many centres. Further controlled studies of methaminodiazepoxide are still required and their results awaited with interest.

Summary

A controlled trial of methaminodiazepoxide 20 mg. three times a day against amylobarbitone 60 mg. three times a day has been performed in neurotic patients complaining of anxiety. The results show highly significantly that patients usually prefer methaminodiazepoxide. Other factors are also discussed.

Acknowledgments

We thank Professor E. Stengel and Dr. W. L. Tonge for their help and advice. We are indebted to the Nursing Staff of the United Sheffield Hospitals for accepting the extra work involved. We are also grateful to Roche Products Limited for providing the materials and advice. Finally we must thank Mrs. E. Alcock for her clerical help.

References

Goodman, L. S., and Gilman, A., *The Pharmacological Basis of Therapeutics*, 1955. 2nd edition. New York: Macmillan Company, p. 138.

Harris, T. H., "Methaminodiazepoxide", *J. Amer. Med. Ass.*, 1960, **172**, 1163.

Hines, L. B., "Methaminodiazepoxide (Librium) a Psychotherapeutic Drug", *Current Therapeutic Research*, 1960, **2**, 227.

Jenner, F. A., Kerry, R. J., and Parkin, D., "A Controlled Trial of Methaminodiazepoxide ('Librium' Roche) in the Treatment of Anxiety in Neurotic Patients", *J. Ment. Sci.*, 1961, **107**, 575.

Raymond, M. J., Lucas, C. J., Beesley, M. L., O'Connell, B. A., and Fraser Roberts, J. A., "A Trial of Five Tranquillizing Drugs in Psychoneurosis", *Brit. Med. J.*, 1957, **2**, 63.

Voelkel, A., "Erfahrungen mit Librium bei psychomotorischen Unruhe- und Angstzuständen", *Med. experiment.*, 1960, **2**, 170.

THE EFFECTS OF MEPROBAMATE ON THE PERFORMANCE OF A FIVE-CHOICE SERIAL REACTION TIME TASK

By

G. S. CLARIDGE, B.A., Ph.D.

Research Associate

Institute of Psychiatry (Maudsley Hospital), University of London

Introduction

The theoretical framework developed by Eysenck (1955) to account for individual differences in motor and other types of performance has, as its main postulate, the statement that extraverts are characterized by high rates and introverts by low rates of inhibitory growth. An extension of this framework (1957) has allowed a link to be made between personality theory and the theory of drug action, since it has been proposed that depressant drugs increase cortical inhibition and so produce extraverted behaviour patterns, while the opposite is true of stimulant drugs. A test of this postulate by Eysenck, Casey and Trouton (1957) suggested that it was essentially confirmed when applied to motor performance. Dextro-amphetamine sulphate was found to improve and sodium amylobarbitone to depress pursuit rotor performance at all stages of practice. It was concluded that the effect of sodium amylobarbitone was to increase the two inhibitory factors recognized by Hullian learning theory, viz. conditioned inhibition (${}_{S}I_{R}$) and reactive inhibition (I_{R}).

More recently Treadwell (1960) has investigated the effects of another depressant drug, glutethimide, and of meprobamate, a tranquillizer, on several psychomotor tasks, including the pursuit rotor. She found that both drugs impaired performance, although glutethimide was consistently more effective in this respect than meprobamate.

The relevance of these two experiments to the present study derives from the fact that Treadwell, in analysing the possible variables underlying her results, departs somewhat from the explanation given by Eysenck *et al.*, for their essentially similar findings. She concludes that depressant drugs impair performance partly because they decrease cortical excitation and hence retard the growth of habit strength, although she points out that this does not rule out a simultaneous effect on the inhibitory variables emphasized by Eysenck.*

The introduction of habit strength as a relevant variable is justified partly by the finding in both studies that depressant drugs do not increase pursuit rotor reminiscence, a measure which has been held to be an index of the amount of I_{R} built up during performance prior to a rest. Treadwell argues, therefore, that either depressant drugs do not increase inhibition, or, if they do, the effect is masked in the reminiscence measure by a simultaneous reduction in habit strength. This masking effect would occur, as she points out, because the degree

* In fact, of course, in formulating his original drug postulate, Eysenck made provision for such a dual effect of drugs on behaviour.

of reminiscence found on the pursuit rotor is partly a function of the amount of habit that has been built up in the pre-rest period.

The difficulties met in these two studies in isolating the variables relevant to Eysenck's drug postulate, when applied to motor performance, are undoubtedly due, in part, to the use of tests such as the pursuit rotor. Here performance is determined by a complex interaction of a number of variables, such as habit, inhibition, and drive, so that adequate indices of the variables involved cannot easily be extracted. This is particularly true of conditioned inhibition; yet a consideration of the role played by this variable would seem to be important in assessing the effect of depressant drugs. If, in fact, an effect of these drugs is a fatiguing or inhibitory one, then one of the experimental results should be an increase in the rest pauses which Bills (1931) demonstrated to be an index of fatigue in continuous work and which, more recently, Kimble (1949) has suggested as a basis for the growth of conditioned inhibition.

A task on which, unlike the pursuit rotor, such rest pauses are detectable is the serial reaction time test. Here the subject is presented with a panel of lights which are illuminated randomly and to which he has to respond by pressing a key appropriate to the light which is illuminated at any one moment. This response extinguishes that light and replaces it with another to which a further response is made, and so on. It has been demonstrated by Broadbent (1958) that measurable gaps in performance occur in most subjects on this type of task. He also reports, furthermore, that the frequency of these gaps is positively correlated with a measure of extraversion, a finding which lends further support to the hypothesis that such rest pauses are relevant to the growth of ${}_{S}I_{R}$.

A further advantage of the serial reaction time task is that, because of its simplicity, initially rapid growth rates of habit strength are unlikely to be major determinants of performance changes*, particularly during the early stages of performance when inhibitory factors have been shown (Ammons, 1947) to reach their maximum. Changes in the measure of performance would, therefore, be expected to reflect increasing amounts of inhibition, unobscured by rapid alterations in habit strength. Evidence that this is so is forthcoming from the work of Venables (1959) who, using the same five-choice task as the one employed here, demonstrated that a consistent pattern of performance in most subjects is a decline from the beginning of the test until about the fifth minute. This is followed by a gradual increase in speed, presumably as habit factors begin to exert a progressively greater influence on performance. Following a factor analysis of various measures from the test, including reminiscence, Venables concluded that fall-off in serial reaction time performance was highly loaded on a factor identifiable as reactive inhibition.

In addition to yielding measures of both inhibitory factors, the five-choice task should also be expected to give an indication of individual differences on the other variable not so far considered in estimations of the effects of centrally acting drugs, viz. the drive (D) variable. It is possible, for example, that the differences in performance level found in the experiments reported by both Eysenck *et al.* (op. cit.) and Treadwell (op. cit.) were due to differences in the level of positive drive. It has recently been shown (Claridge, 1960), for instance, that a factor identifiable as drive has loadings on the overall level of performance reached on the pursuit rotor. Nevertheless, a satisfactory measure of D is not

* In this respect it is similar to the more usual type of vigilance test, where habit strength may be said to be near its maximum at the very beginning of performance. The similarities between the two types of test have, in fact, already been extensively commented upon by Broadbent (1958).

readily obtainable from the latter test. The strength of drive is clearly reflected most directly in performance during those responses occurring at the beginning of a task, i.e., before the other variables of habit and inhibition have had an opportunity of influencing behaviour. Yet on such complex tasks as the pursuit rotor all subjects necessarily start at zero or near-zero level, so that subjects are not differentiated until a relatively late stage of performance. The ability of the five-choice test to yield a substantial score at the beginning of practice should, on the other hand, allow us to extract from the task an index of individual differences in drive level and, therefore, to investigate the effects of drugs on this variable.

The aim of the study reported here was, therefore, to investigate the effects of meprobamate on motor performance, using a suitable experimental tool which allowed the relevant variables to be isolated more easily than hitherto. The hypotheses to be tested were derived directly from Eysenck's drug postulate, particularly that part of it which relates to the effect of depressant drugs on the cortical inhibitory processes. The following predictions were made:

(*i*) There would be no difference in starting level under drug and placebo conditions. Although the possibility has been considered that an effect of the drug would be to reduce drive level, there was, in fact, no reason *a priori* for assuming that such would be the case.

(*ii*) Fall-off in performance from the beginning of practice would be greater under drug than under placebo conditions. Because of this the difference between the two conditions should be more evident at the end than at the beginning of the performance period.

(*iii*) The amount of reminiscence after a rest would be greater under drug than under placebo conditions.

(*iv*) The number of gaps in performance would be greater under drug than under placebo conditions. Again this should be more evident at the end than at the beginning of performance.

Description of Subjects

The subjects used were twenty male soldiers, all volunteers, who were employed as either male nursing orderlies or clerks, or on general duties in a military psychiatric hospital. These were allocated at random to two experimental groups: Group D receiving meprobamate and Group P a placebo. The mean age of Group D was 21·5, S.D. 1·29 years and of the P group 26·1, S.D. 7·02 years. The 1956 revision of Raven's Progressive Matrices was given to all subjects and the mean IQ's of Groups D and P were, respectively, 106·1, S.D. 6·76 and 108·1, S.D. 12·16. Because personality factors, particularly with regard to extraversion, were likely to influence the results, the Maudsley Personality Inventory (MPI) (1959) was administered to each subject during the testing session. The mean extraversion (E-scale) score for Group D was 30·2, S.D. 6·26 and that of Group P 29·2, S.D. 5·09. On the neuroticism (N) scale Group D had a mean score of 24·2, S.D. 8·77 and Group P a mean score of 22·7, S.D. 11·56. The two groups were thus very comparable with respect to age, IQ, and personality assessment.

Description of Apparatus

As already noted, the task was a five-choice serial reaction time test, the apparatus being constructed by P. H. Venables from a design based partly on

that described by Leonard (1953). It consisted of a display panel set at 15 degrees from the vertical and containing five lights placed 2 in. apart in a horizontal row. In front of each light and in the horizontal plane was a key 5 in. long and $1\frac{3}{4}$ in. wide. As we have described previously, the subject is asked to press the key corresponding to the light which is lit, thus extinguishing it and illuminating another light to which a further response is made, and so on. The order in which the lights were illuminated was a random one over a series of 50, except that no light appeared twice in succession. Subject's response, both correct and incorrect, were registered on a moving drum event recorder and, in addition, a simple counter included in the circuit allowed the experimenter to note down scores for each minute of performance.

Experimental Procedure

All subjects were administered three tablets a day for a period of three days. This is a common clinical dosage which it was hoped would simulate clinical conditions of usage more closely and have a more clear-cut effect on performance than the single tablet often used in this kind of experimental study.

In the case of Group D each tablet contained 400 mg. of meprobamate so that prior to the testing session subjects in this group had consumed 3·6 g. of the drug. The tablets administered to Group P were inert, but identical in appearance with those given to Group D. The subjects were unaware that some of the tablets used were inert; they were told simply that the aim of the experiment was to investigate the effects of a commonly used drug.

Each subject was given a written schedule of the hours at which he was to take each tablet. These were 6 a.m., 10 a.m., and 2 p.m., the subject coming for testing as far as possible about one hour after taking the last tablet on the third day. After a brief demonstration of the procedure, he was given half-a-minute's practice to make sure that he was familiar with the instructions. He then worked for ten minutes on the test, followed by a rest of five minutes, during which time he completed the personality questionnaire. Following the rest, the subject then worked for a further period of one minute so that a reminiscence score could be obtained.

Results

The results are shown graphically in Figure 1 where the group mean scores for each minute of the work period are plotted. Also included in this figure are similar group means for the first ten minutes' work of a further group of twenty subjects, who, before the present experiment was undertaken, had performed for twenty minutes on the task under identical conditions, but without any treatment at all. Although it had not been anticipated before the drug study that these results would be included in the analysis, certain obvious trends in the data, apparent prior to statistical analysis, indicated the undoubted importance of a comparison between such a group and the two treatment groups. The twenty subjects involved in this group—hereafter called Group NT—were selected from the same army population as those used in the drug investigation. Indeed, they are highly comparable to Groups D and P on the four variables which we considered relevant. The mean age and IQ for the NT group were, respectively, 22·0, S.D. 2·07 years, and 106·2, S.D. 19·58. On the MPI their mean E-scale score was 31·0, S.D. 6·93 and their mean N-scale score 21·5, S.D.11·72.

Inspection of Figure 1 reveals a number of quite clear trends. It is apparent, for instance, that Group NT is superior in performance at all stages to both Groups D and P who tend to resemble each other closely. Group NT shows the kind of performance pattern expected in this task, i.e., an abrupt fall in performance followed by a gradual rise up to the tenth minute, a pattern also shown by Group P but not by Group D who continue to fall in the latter half of the test.

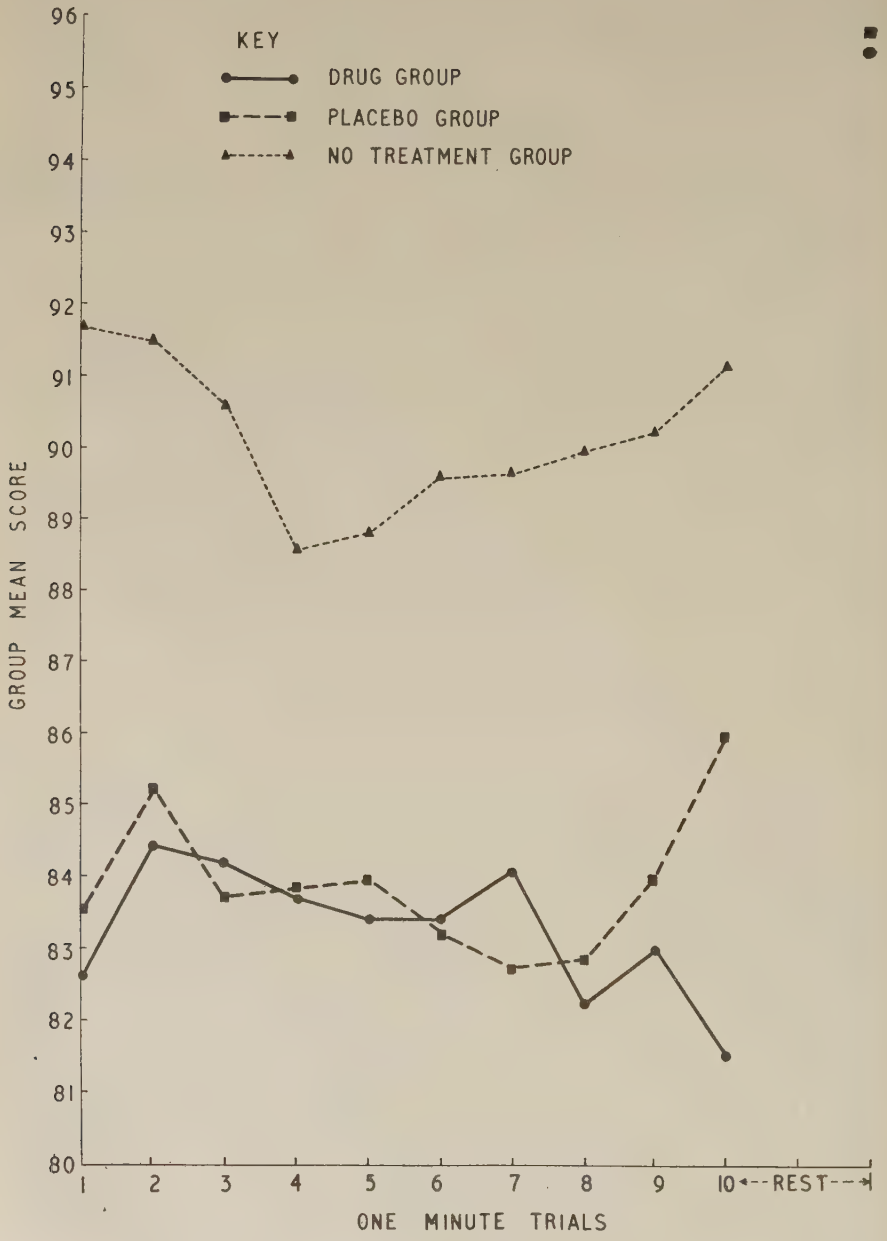


FIG. 1.—Mean score for each group on each trial.

In order to consider the significance of these trends the data relevant to each of the predictions made will be considered separately in turn. For the purpose of statistical analysis of the performance curves linear regression lines were fitted to the data, the first and second five minutes of the work period being considered seaparately. This technique yielded two measures for each subject, a coefficient "b" representing performance *level*—starting level in the case of the first half of performance—and a coefficient "a" representing rate of change per trial or, in the case of negative values, fall-off in performance. The group means for these two coefficients for the first and second halves of the task are shown in Table I.

TABLE I

Mean slope ("a") and mean initial response speed ("b") for each group during each half of the work period

First five minutes

	Group D		Group P		Group NT	
	"a"	"b"	"a"	"b"	"a"	"b"
Mean	+0·07	83·45	—0·06	84·20	—0·92	92·92
S.D.	1·246	7·668	1·557	5·868	1·493	11·197

Second five minutes

	Group D		Group P		Group NT	
	"a"	"b"	"a"	"b"	"a"	"b"
Mean	—0·46	84·20	+0·73	82·69	+0·36	89·08
S.D.	0·721	9·983	0·944	6·958	1·244	12·096
	N = 10		N = 10		N = 20	

Starting level. The relative starting levels of the three groups illustrated in Figure 1 are also reflected in the group mean values of the "b" coefficient for the first half of the work period (see Table I). There was no difference between Groups D and P in starting level, "t" between the appropriate "b" values for these groups reaching only 0·233, which is non-significant (d.f. 18). While this finding is in line with our prediction for this measure, it cannot be accepted entirely on its face value, since both treatment groups were alike in starting at a significantly lower performance level than the no treatment group. The value of "t" when Group NT is compared with the combined drug and placebo groups was 2·9470, $p<0·01$ (d.f. 38). Thus, while it is evident that a significant reduction occurs in the starting level of the group receiving meprobamate, the effect is, in fact, no greater than that produced by an inert substance. On the other hand, the general effect of "treatment" does seem to be one of reducing starting level and possibly, therefore, of lowering drive.

Performance fall-off. While it was predicted that the rate of fall-off from the beginning of the test would be greater in the drug than in the placebo group, the "a" coefficients for the first half of the task (see Table I) indicate that, at least during this period, such was not the case. The difference between these measures for Groups D and P was not significant, "t" equalling only 0·193 (d.f. 18). The relative lack of fall-off shown by the two treatment groups stands in marked contrast to the rapid decline found in the no treatment group. The result is, however, in keeping with Venables' report (1959) that starting level and fall-off on this task are positively correlated, a finding which has appeared

also in the writer's work on two subsequent occasions (Claridge, 1961; Claridge and Herrington, 1960). Generally speaking the effect would seem to be due to the greater absolute amount of inhibition which is necessarily associated with a higher number of initial reponses. This will tend, therefore, to have a proportionally greater decremental effect on the subsequent response rate. Thus, any effect, in the present experiment, of the drug on the inhibitory processes may well have been masked in the early stages by the marked lowering of response rate which occurred in the two treatment groups.

When we turn, however, to the second half of the work period, more evidence of a drug effect appears. The atypical decline shown by Group D in Figure 1, is reflected in a mean for the "a" coefficient during this period of —0·46, compared with a mean for Group P of +0·73. The difference between these two groups on this measure was significant at the 0·01 level, "t" being 3·005 (d.f. 18). This confirms our prediction that the effect of meprobamate would be greatest towards the end of performance. Had the experiment been carried further it is probable that this effect would have been even more evident.

Reminiscence. The mean reminiscence score for Group D was 14·0, S.D. 6·21 and for Group P 9·4, S.D. 6·62. There was, therefore, as predicted, a greater amount of reminiscence in the drug group than in the placebo group. The difference failed, however, to reach significance at the 0·05 level, "t" being 1·520 (d.f. 18). Nevertheless, as can be seen from Figure 1 this difference in reminiscence was sufficient to bring the performance levels of the two treatment groups together in the post-rest period. This suggests that the pre-rest decline in Group D was due, as we proposed, to a greater accumulation of inhibition and not to a depressive effect of the drug on habit strength. In other words, given a sufficient rest and time for inhibitory factors to dissipate, the drug group is capable of performing at a level equal to that of the placebo group. Unfortunately, no comparison was possible between these two groups and Group NT since the latter had performed continuously for twenty minutes and so their reminiscence score could not be considered equivalent. However, such a comparison would not alter the conclusion that, at the performance level found in the two treatment groups, meprobamate does not, on this task at least, influence habit growth directly.

Gaps in performance. Although it had originally been intended to take as an index of gaps in performance a measure of actual rest pauses it was subsequently decided that errors provided a clearer and more reliable indication of this aspect of the results. It was quite apparent, as was noted by Broadbent (1958), that in normal subjects, errors invariably accompanied measurable breaks in performance on this task, and in so far as the former were discrete and easily recognizable items a measure of them was obtainable more readily than was the case with rest pauses, where an arbitrary criterion of a rest was necessary. Although theoretically an error may be considered different from a rest pause occurring without an error, in terms of their hypothesized role of dissipating *centrally-accumulated* inhibition, there seems little basis for distinguishing between them. A graphical representation of both measures indicated that they behaved similarly and, as can be seen from Figure 2, the change in error score throughout the test for the three groups followed very closely the pattern expected from our hypothesis that gaps in performance are a basis for the growth of conditioned inhibition. Errors can be seen to increase rapidly from the beginning of performance, reaching an asymptote during the second half of the test. In fact, the negatively accelerated curve for each group is very

similar to that presented by Kimble and Shatel (1952) in their analysis of inhibition in pursuit rotor learning.

A comparison between the groups indicates that, paralleling the data for correct responses, the difference between the drug and placebo groups becomes

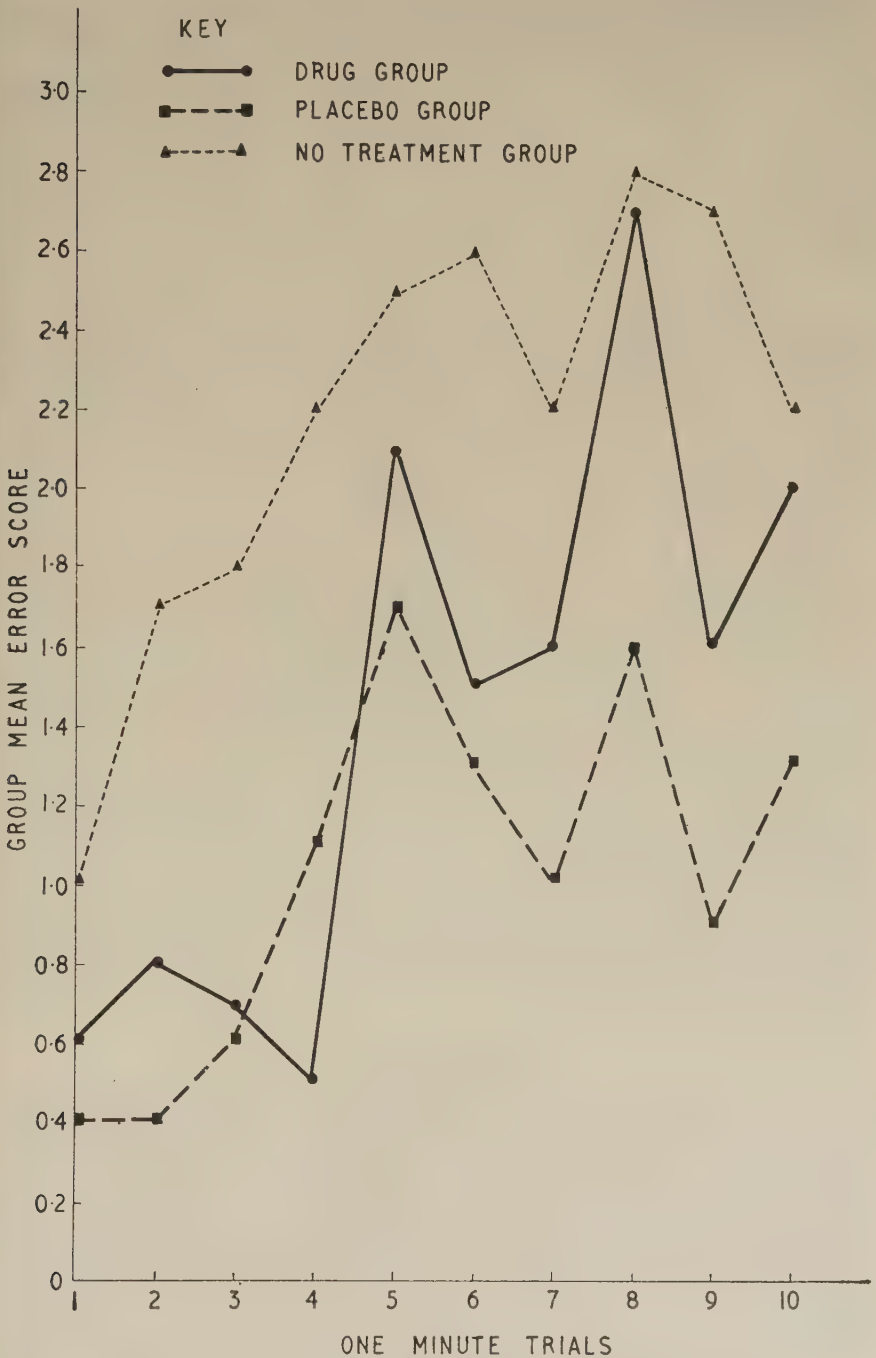


FIG. 2.—Mean errors for each group on each trial.

apparent only during the second half of the test when Group D reaches a higher asymptote of errors than Group P. Still higher at all stages of performance is Group NT, this confirming the suggestion made earlier that, other things being equal, high response rates will tend to be associated with greater absolute amounts of inhibition.

Dividing the data into two halves, as before, the following group mean error scores for the first and second five minutes of the test were obtained:

	1st five minutes		2nd five minutes	
	Mean	S.D.	Mean	S.D.
Group D	4·7	2·24	9·4	5·31
Group P	4·2	3·09	6·1	2·91
Group NT	9·0	8·67	12·4	14·33

Analysis of variance of the data for the second five minutes of performance indicated that the difference between the groups was not significant. No further calculations were, therefore, carried out. Although the fourth prediction that there would be an effect of the drug on performance gaps was not clearly confirmed, the trends in the results suggested that, had the experiment been carried further, significant differences would probably have been found, since at the point at which the experiment was terminated the curves for errors in the two treatment groups were beginning to diverge markedly.

Finally, it is of interest to consider the extent to which errors or gaps account for the performance changes illustrated in Figure 1. It might be argued, for instance, that the initial decline in correct responses, shown most clearly in Group NT, and the continued fall-off of Group D in the second half of the test are accounted for *solely* by the simultaneous increase in errors. That this is not so is demonstrated in Figure 3 where total responses, i.e., correct plus incorrect, are plotted for each group. The curves shown here closely parallel those found in Figure 1, suggesting that there is, over and above the decremental effect of errors, a gradual decline in overall response rate due to the accumulating effects of reactive inhibition, which is ultimately dissipated in the post-rest period. The decline in correct responses can thus be seen to be the result of the combined effects of both types of inhibition, reactive and conditioned. This presumably accounts for the fact that, while the two treatment groups are not discriminated significantly on measures of these variables taken separately, viz., on reminiscence and errors, they do differ significantly on the measure of performance fall-off, which reflects the influence of both factors.

Discussion

An interesting feature of the results which requires further comment is the depressing effect on performance of the placebo. The ameliorating effect of inert substances in psychiatric practice is, of course, by no means rare, as Trouton's review of the topic (1957) has emphasized. The extent to which the performance of normal subjects was affected was, however, perhaps a little surprising. One reason was almost certainly the sample's sophistication with regard to drugs. Some of the subjects were in daily contact with patients receiving medication, while even the fact of working on general duties in a psychiatric hospital would tend to make others more than usually familiar with the effects of drugs. This heightened suggestibility was reflected in the reports received

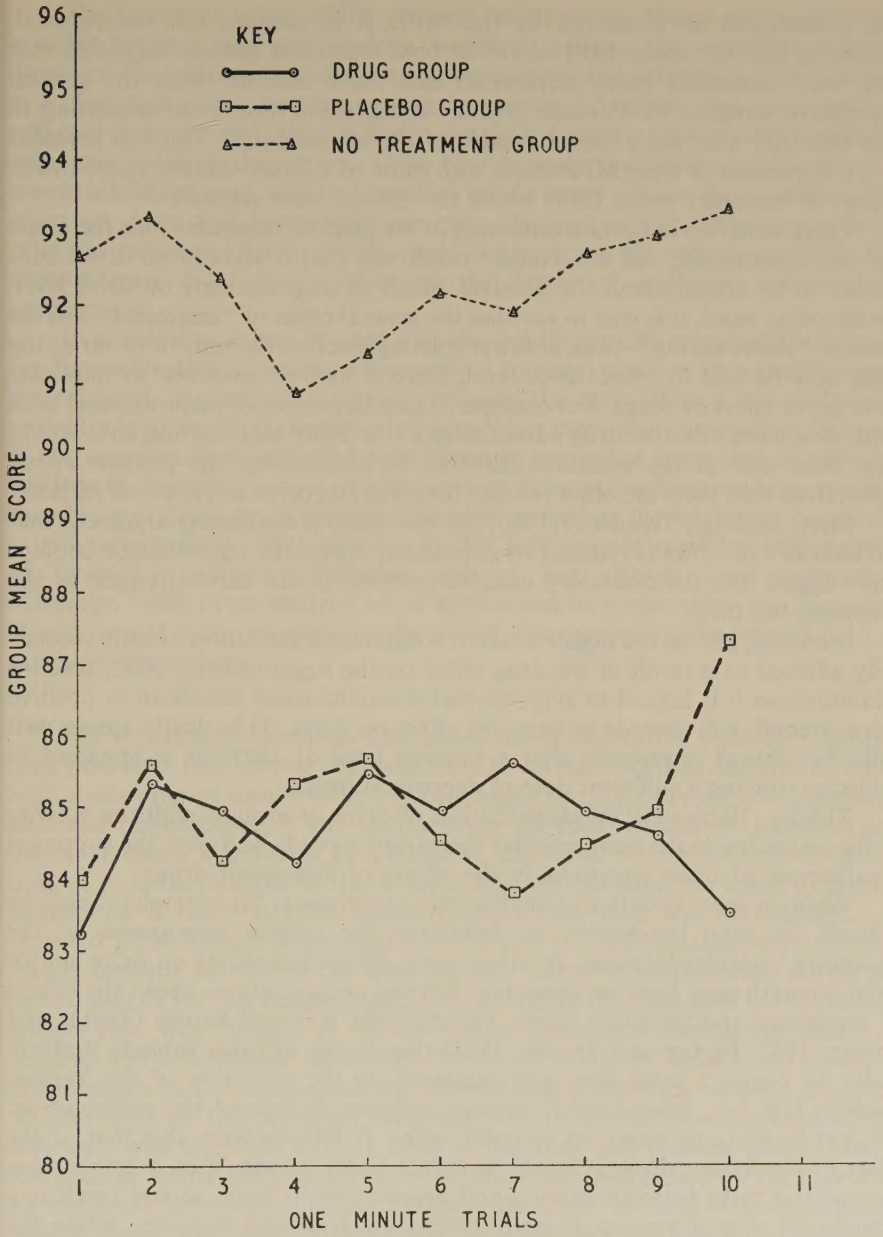


FIG. 3.—Mean total responses (correct + incorrect) for each group on each trial.

from some subjects taking part in the placebo group that they had had odd sensations of drowsiness and so on after taking the tablets given to them.*

Another factor probably affecting the placebo effect was that of personality. There is some, although not consistent, evidence from the work of Knowles and Lucas (1960) that degree of placebo response is positively related to extraversion

* It is interesting that the reported sensations were all in terms of drowsiness rather than alertness. This may be explained by the fact that to the layman "being drugged" more often indicates anaesthetization than vice versa.

and neuroticism as measured by the MPI. It is perhaps not coincidental, therefore, that the mean MPI scores of both treatment groups suggested that they were somewhat more extraverted and more neurotic than the general population sampled by Eysenck (1959). At the same time, it is interesting to note that they were not a biased sample of the hospital staff. This was revealed by a comparison of their MPI scores with those of a larger sample, made by the writer, of the army corps from which the groups were selected.

There were two important outcomes of the placebo response—one fortunate and one unfortunate. An unfortunate result was that it allowed no direct conclusion to be drawn about the possible effects of meprobamate on drive level. On the other hand, it is true to say that the general effect of "treatment"—in the sense of "tablet-taking"—was to lower starting level on the test. In so far as the latter may be said to reflect drive level, there is indirect evidence to implicate drive in the effect of drugs. For example, had a large dose of meprobamate been used, or a more effective drug administered, it is likely that starting level would have been one of the measures involved in overcoming the placebo effect. Apart from this, there are other reasons for accepting drive as a relevant variable.

First, although Treadwell (1960) has presented a convincing argument that the level of excitation is reduced by depressant drugs, the reminiscence findings here suggest that the excitatory variable involved is not habit strength, as she proposes, but drive.

Secondly, just as the negative habit, conditioned inhibition, is only secondarily affected as a result of the drug effect on the negative drive state, reactive inhibition, so it is logical to suppose that a simultaneous reduction in positive drive strength will precede in time any effect on habit. This clearly agrees well with the clinical impression that a lowered level of alertness is apparent in subjects receiving a sufficient dose of depressant drugs.

Thirdly, Hebb's (1955) identification of drive or arousal with the activity of the ascending brain stem reticular formation accords well with the supposed involvement of these structures in the effects of depressant drugs.

While in some situations (conditioning experiments for example) it may be difficult, or even impossible, to determine the relative importance of the excitatory variables involved, in other cases differential effects on drive and/or habit strength may have an important bearing on predictions about the effects of depressant and stimulant drugs. For example, it is well known (Taylor and Spence, 1952; Farber and Spence, 1953) that highly anxious subjects perform badly on complex tasks due, it is supposed, to the operation of the Yerkes-Dodson law, i.e., drive level in anxious subjects is beyond the optimum for efficient learning to occur on complex tasks. It follows from this that, if the effect of depressant drugs is imply to reduce habit growth, then a comparison on complex tasks between anxious and non-anxious subjects should result in a retardation of performance in both groups which should, however, retain the same positions in relation to each other. On the other hand, if depressant drugs reduce drive, then both groups should, as before, show retarded learning, but in this case the performance of anxious subjects should be equal to, or even better than, that of non-anxious subjects, because the drug should have reduced the drive level of the former to a point nearer to the optimum level for efficient acquisition. Each of these predictions could quite easily be tested experimentally and the result of such an investigation would be expected to throw considerable light on the precise effects of centrally acting drugs on the excitation level. Particularly relevant in this context would be the tranquillizers, which are aimed clinically at the reduction of anxiety symptoms.

The fortunate result of the placebo response was that a comparison was possible between drug and no-drug conditions without the complication introduced by the relationship between response speed and inhibition. For example, it is clear that in the no-treatment group greater inhibition was generated—as reflected in errors and initial fall-off—simply by virtue of the greater number of responses made in this group. Thus, the tendency for depressant drugs to increase inhibition may well be cancelled out in many studies by a simultaneous effect on drive and hence response rate. Because in the present experiment response rate was—inadvertently—held constant, we are able to conclude that meprobamate did have an effect on the degree of inhibition produced by performance.

In conclusion, it can be said that the results provide considerable support for Eysenck's drug postulate when applied to serial reaction time performance. As expected, the use of a simple vigilance-like task allowed the underlying variables involved to be investigated somewhat more thoroughly than hitherto. If the interpretation presented here diverges somewhat from that of previous workers in Eysenck's school, it is because an attempt has been made to appraise the effects of drugs on excitatory variables, as well as the inhibitory ones most usually emphasized. That workers in this field should consider both aspects of Eysenck's excitation-inhibition concept has already been emphasized (Claridge, 1960) in an analysis of its application to personality. The same conclusion would seem to apply to the use of the concept in the related field of psychopharmacology.

Summary

The experiment described here arose out of two earlier tests of Eysenck's drug postulate that central depressant drugs increase cortical inhibition. While both studies report similar effects of depressant drugs on pursuit rotor performance and reminiscence, it was unclear from the data whether the impaired performance found was due to an increase in inhibition or to a decrease in excitation, or to both. In order to throw some light on this issue, the effect of meprobamate on a more suitable serial reaction time task was investigated. As expected from Eysenck's postulate, the effects of meprobamate were revealed mainly towards the end of the work period, fall-off in performance during the second half of the test being significantly greater in the drug than in the placebo group. This was thought to be due to the combined cumulative effects of reactive and conditioned inhibition. Measures of these variables in terms of reminiscence and errors respectively showed that differences between drug and placebo were in the predicted direction, but in neither case significant. No difference was found in starting level in the drug and placebo groups, but a comparison with a third group who had previously performed on the task with no treatment indicated a marked "placebo reaction" in those receiving dummy tablets. There was sufficient evidence from the data for the three groups to conclude that an effect of central depressants is probably to decrease excitation as well as increase inhibition. It was suggested, however, that the appropriate excitatory variable involved was drive rather than habit strength, as previously emphasized. The hypothesis was proposed that the habit variables, ${}_{S}H_{R}$ and ${}_{S}I_{R}$, were secondarily affected following a primary effect on the drive variables, D and I_{R}.

Acknowledgments

The author wishes to acknowledge the co-operation of Colonel J. McGhie, Commanding Officer at the Royal Victoria Hospital, Netley, who supplied the subjects used in this study. The work was made possible by a grant from the Wallace Laboratories.

References

AMMONS, R. B., "Acquisition of motor skill. II. Rotary pursuit performance with continuous practice before and after a single rest", *J. exp. Psychol.*, 1947, **37,** 393–411.

BILLS, A. G., "Blocking: a new principle of mental fatigue", *Amer. J. Psychol.*, 1931, **43,** 230–45.

BROADBENT, D. E., *Perception and communication*, (1958). London: Pergamon Press.

CLARIDGE, G. S., in Eysenck, H. J. (Ed.), *Experiments in personality*, 1960. London: Routledge & Kegan Paul.

Idem, "Arousal and inhibition as determinants of the performance of neurotics", *Brit. J. Psychol*, 1961 (in press).

Idem, and HERRINGTON, R. N., "Sedation threshold, personality, and the theory of neurosis", *J. Ment. Sci.*, 1960 (in press).

EYSENCK, H. J., "A dynamic theory of anxiety and hysteria", *J. Ment. Sci.*, 1955, **101,** 28–51.

Idem, "Drugs and personality: I. Theory and methodology", *J. Ment. Sci.*, 1957, **103,** 119–31.

Idem, Manual, *The Maudsley Personality Inventory*. 1959. London: University of London Press.

Idem, CASEY, S., and TROUTON, D. S., "Drugs and personality: II. The effect of stimulant and depressant drugs on continuous work", *J. Ment. Sci.*, 1957, **103,** 645–49.

FARBER, I. E., and SPENCE, K. W., "Complex learning and conditioning as a function of anxiety", *J. exp. Psychol.*, 1953, **45,** 120–25.

HEBB, D. O., "Drives and the CNS (Concepual Nervous System)", *Psychol. Rev.*, 1955, **62,** 243–54.

KIMBLE, G. A., "An experimental test of a two-factor theory of inhibition", *J. exp. Psychol.*, 1949, **39,** 15–23.

Idem, and SHATEL, R. B., "The relationship between two kinds of inhibition and the amount of practice", *J. exp. Psychol.*, 1952, **44,** 355–59.

KNOWLES, J. B., and LUCAS, C. J., "Experimental studies of the placebo response", *J. Ment. Sci.*, 1960, **106,** 231–40.

LEONARD, J. A., "Advance information in sensori-motor skills", *Quart. J. exp. Psychol.*, 1953, **5,** 141–49.

TAYLOR, J. A., and SPENCE, K. W., "The relationship of anxiety level to performance in serial learning", *J. exp. Psychol.*, 1952, **44,** 61–64.

TREADWELL, E., *in* EYSENCK, H. J. (Ed.), *Experiments in Personality*, 1960. London: Routledge & Kegan Paul.

TROUTON, D. S., "Placebos and their psychological effects", *J. ment. Sci.*, 1957, **103,** 344–54.

VENABLES, P. H., "Factors in the motor behaviour of functional psychotics", *J. abnorm. soc. Psychol.*, 1959, **58,** 153–56.